British Journal of Diseases of the Chest

EDITORS
J. R. BELCHER and J. SMART

Volume LV No. 4 October, 1961

PUBLISHED QUARTERLY BY
BAILLIÈRE, TINDALL & COX
7 and 8 Henrietta Street, London, WC2

British Journal of Diseases of the Chest

Incorporating the British Journal of Tuberculosis and Diseases of the Chest

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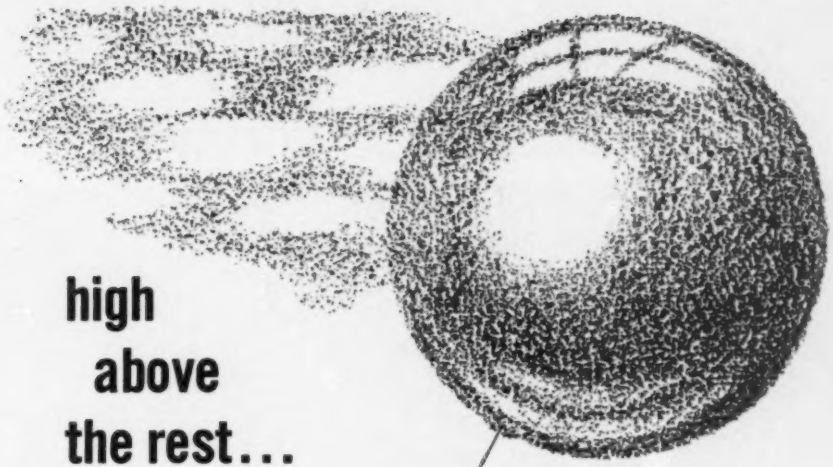

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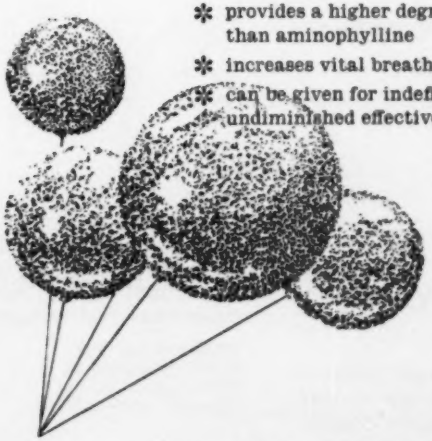

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PULMONARY TUBERCULOSIS IN INDIA

By B. G. Prasad

From the Department of Social and Preventive Medicine,
King George's Medical College, Lucknow, India

Introduction

Tuberculosis is a major public health problem in India. In 1951 the population was 357 million, and tuberculosis is responsible for half a million deaths each year. Until recently malaria was the most important cause of death, being responsible for more than one million deaths a year. With the introduction of the national malaria control programme in 1952 and the national malaria eradication programme in 1958, a steep fall occurred in the mortality from that disease, and tuberculosis has now become the commonest cause of death. Next is smallpox causing nearly 70,000 deaths a year. Other important causes of death are cholera and plague. As against 300,000 deaths a year from cholera in India a decade ago, there were 67,000 deaths in 1958. Plague, which used to cause on an average 21,000 deaths a year between 1939 and 1948, was responsible for only 178 deaths in 1955 and now it has almost disappeared.

The ancient literature and the various writings of the indigenous *Ayurvedic* system of medicine indicate that tuberculosis was known in India more than 2,000 years ago. The principal diseases which occur in Vedic medical texts are: fever, diarrhœa, cough, consumption, dropsy, sores, abscess, tumour, leprosy, skin diseases, inherited diseases and "seizures" by various demons (Zimmer, 1948). The description of the symptoms of pulmonary tuberculosis and its treatment leaves no doubt about its identity, but this literature does not give any idea of the magnitude of the tuberculosis problem in the community.

Present Position

Until a few years ago accurate information about the extent of tuberculosis in the country was not available, though enough evidence could be got from mortality statistics, from hospital figures, and from a few isolated surveys carried out in special groups, to suggest that the disease was widespread and constituted a problem of great magnitude. The system of medical certification of the cause of death does not exist in India and reporting of the cause of death is done by a lay agency. Registration of the cause of death is therefore neither complete nor accurate. The extent of under-reporting in the registration of deaths in 7,772 villages in 44 districts of the State of Uttar Pradesh was found to be 24·3 per cent. (Prasad, 1952). It is also not uncommon for tuberculosis to be mistaken for some other disease. For example, in a

(*Received for publication May* 15, 1961.)

village several people who had suffered from chronic fever and had died were reported to have died from tuberculosis, but on investigation it was found to have been kala-azar (Prasad, 1949). Routine vital statistics therefore do not give reliable information on mortality.

Morbidity estimates of the disease were also not reliable because facilities for proper diagnosis and notification have not existed, particularly in rural areas where 82·7 per cent. of the population lives and no systematic surveys have been done. A few special surveys carried out on limited groups of population provided some indication on the prevalence of tuberculosis. In 1938 and 1939 a population of 30,000 in Saidapet in South India was tuberculin tested and those who were strongly positive to tuberculin were X-rayed. The rate of prevalence of tuberculosis was found to be 2·3 per cent. (Benjamin *et al.*, 1939). Another survey in Serampore in Bengal showed a morbidity rate of 7 per cent.; tubercle bacilli were demonstrated in 3 per cent. of the population examined (Lal *et al.*, 1943). Without mass miniature X-ray equipment, these investigations on urban populations were carried out with meagre X-ray facilities. In 1952 a rural population of 35,000 persons living in 175 villages around Madanapalle in South India was surveyed using miniature X-rays. The morbidity in this group was 0·42 per cent.; tubercle bacilli were demonstrated in 0·24 per cent. (Frimodt-Moller *et al.*, 1952). Although these studies gave valuable information, they did not provide an adequate basis for estimating the incidence of tuberculosis in the population as a whole.

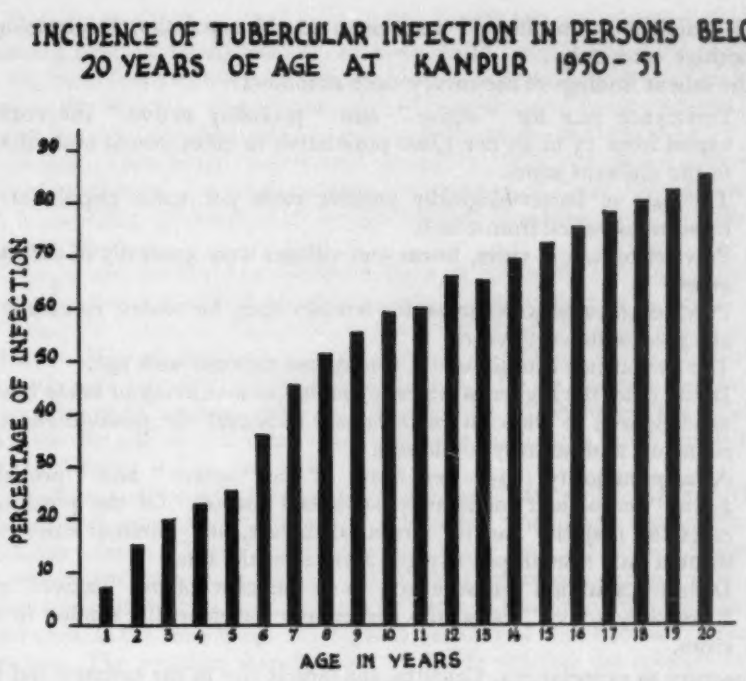
The infection rate may be a good index of the prevalence of the disease. The rates revealed by a tuberculin survey carried out between 1949 and 1951 in Uttar Pradesh (the State contains 17·7 per cent. of India's population) were as follows:

TABLE 1.—POSITIVE TUBERCULIN TEST RATES IN URBAN AND RURAL POPULATION OF UTTAR PRADESH, 1949-51

Age group	*Positive tuberculin test rate percentage*	
	Urban	*Rural*
0-6 years	23·0	18·0
7-14 years	56·7	43·7
+ 15 years	75·0	59·0

These were done under the auspices of W.H.O./Government of India/State Government in connection with the mass BCG vaccination campaign, started in 1952.

The infection rate is higher in the towns than in the country, but the differences in rates are not as well marked as was expected. In industrial cities in India about 75 per cent. of the population became positive by the age of 15. The rates shown by a survey carried out in the industrial city of Kanpur in Uttar Pradesh in 1950-51 in children are given in the accompanying chart (Mahrotra, 1960).



NATIONAL TUBERCULOSIS SAMPLE SURVEY, 1955-58

Since large-scale tuberculosis control measures were being introduced as part of the Five Year Plans in India, it was thought essential to secure adequate data which could not only help in introducing control measures, but which could also provide the base line for assessing the effectiveness of these measures. It was felt that without such data the opportunity for scientific assessment might be lost. The Tuberculosis Sub-committee of the Indian Council of Medical Research decided that this objective could be achieved only by undertaking a sample survey in different parts of the country. The survey was completed in 1955-58 (Indian Council of Medical Research, 1959) and was the first major attempt at a systematic assessment of the magnitude of the tuberculosis problem in India.

The survey covered six zones (Calcutta, Delhi, Hyderabad, Madanapalle, Patna and Trivendrum). 290,758 people above the age of 5 years were X-rayed on miniature 70 mm. film (it was possible to X-ray 90 per cent. of the sampled population in most of the zones), in 6 cities, 30 towns and 151 villages. In all cases showing evidence of abnormality in the X-ray film, the sputum was examined by staining and by culture, and laryngeal swabs were taken for culture. Indices used for assessing prevalence of morbidity were:

(1) Number of "active" and "probably active" cases per 1,000 of population (*i.e.* total of bacteriologically and radiologically positive cases).

(2) Number of " bacillary " cases per 1,000 of population (bacteriologically positive cases only).

The salient findings of the survey were as follows:

1. Prevalence rate for " active " and " probably active " tuberculosis varied from 13 to 25 per 1,000 population in cities, towns and villages in the different zones.
2. The rate of bacteriologically positive cases per 1,000 population in these areas varied from 2 to 8.
3. Prevalence rate in cities, towns and villages were generally of the same order.
4. Prevalence rates were lower for females than for males, especially in age groups above 35 years.
5. The prevalence rate showed a continuous increase with age.
6. In the cities the higher prevalence among persons living in *kutcha* houses as compared to those in *pukka* houses indicated the possible effect of economic and sanitary conditions.
7. A large majority (39-80 per cent.) of the " active " and " probably active " cases had moderately advanced disease. Of the remaining cases the majority had far advanced disease, and minimal cases constituted only a small percentage (2 to 12) of the total.
8. Definite cavitation was seen in 4 to 33 per cent. of the " active " and " probably active " cases; this percentage was generally smaller in the cities.

Contrary to expectations, Calcutta, the largest city in the country, did not show a particularly high prevalence rate. " Active " and " probably active " prevalence rate was 16·7 per 1,000 population and the rate of bacteriologically positive cases was 6·4 per 1,000. There were wide variations in the morbidity rates between the blocks in the cities. In Calcutta, for instance, there were blocks showing a prevalence of over 50 per 1,000, whereas there were others in which the prevalence was only 3 per 1,000. These wide variations and the presence of pockets with high prevalence indicate the need to undertake further investigations in order better to understand the epidemiology of the disease in the bigger cities.

Anti-tuberculosis Programme

It is estimated that in India there are about 2·5 million open cases of tuberculosis and nearly half a million people die annually from it (Benjamin quoted by Health Survey and Development Committee, 1946); 7 to 8 per cent. of all deaths and 20 per cent. of deaths from respiratory diseases in India are from tuberculosis. The disease kills on an average one person every minute in India. The mortality rate is about 150 per 100,000 of the population. There are cities which have nearly twice or three times this rate. Kanpur and Lucknow have a rate of over 400 and Calcutta a rate of 250 per 100,000 of the population. Tuberculosis is estimated to cause a loss of about 1,000 million man-days or 2,000 million rupees* annually (Benjamin, 1958).

* One rupee is equal to 1s. 6d. or nearly one-fifth of an American dollar.

Western standards require one bed in a hospital or a sanatorium for every thousand head of population, or for each death from tuberculosis per year. On this basis India would need 500,000 beds for tuberculosis alone. The health panel of the Planning Commission of the Government of India estimated that at least 4,000 Tuberculosis Clinics, 500,000 beds, 15,000 doctors, 50,000 trained nurses and 12,000 home visitors were needed to tackle the disease effectively. These needs would cost a non-recurring expenditure of about Rs.4,500 million and a recurring expenditure of Rs.600 million (Benjamin, 1958) (2 Rs. per head per year).

The annual income (*per capita*) in India is Rs.293·60 (1958-59) and it is no wonder that expenditure on tuberculosis control at present is only Rs.0.05 per head per annum. The total expenditure on medical care and public health *per capita* per annum is less than 2 rupees in majority of the states, which is less than 10 per cent. of their total revenue. To get voluntary donations, a campaign is being organised every year by the Tuberculosis Association of India for the sale of T.B. Seals costing Rs.0·10 each, and this helps to bring additional funds.

To get enough beds for institutional care would have taken several decades. In 1947 there were only 113 Tuberculosis Clinics, 7,000 beds, 250 doctors and 500 home visitors. There was hardly one X-ray unit for each 2 million of the population. It was no wonder that of the tuberculosis patients who went to the clinics for the first time, 54 per cent. were in an advanced stage and only 14 per cent. in the early stage. By 1958 the number of beds had been increased to 25,000. The problem therefore was to decide whether the country should try to set up a complete service, or to do something practical, less costly and capable of being introduced in a comparatively short time with reasonable chance of checking the spread of this disease. The Government of India have decided to expand domiciliary services through Tuberculosis Clinics and to intensify the programme of BCG vaccination in the population on a large scale. When tuberculosis is widespread and the chances of everyone getting infection are great, it is desirable to protect those who are uninfected, by BCG vaccination. The Government of India realises the limitation of this vaccination, but it can be extensively used as a protection against tuberculosis in a comparatively short time and at low cost.

BCG vaccination was introduced in 1948 and expanded into a mass campaign in 1951. With the help of the International Tuberculosis Campaign (which includes UNICEF), a BCG Vaccine Laboratory was established at Guindy, near Madras, in 1948. The laboratory is the world's largest production centre of BCG vaccine. It produces 25 million doses of the vaccine every month. It not only caters for the needs of India, but also for those of the neighbouring countries of South-East Asia on a non-profit basis. At present it is producing only wet vaccine, but the laboratory is expected to produce and distribute freeze-dried vaccine in the near future. This will be a great advantage in a rural country like India.

BCG vaccination was started on a small scale in 1948 at two centres, Madanapalle (Madras) and Delhi, but since there was good response from the

general public, it was extended first to the States of Uttar Pradesh, the Punjab and Madhya Pradesh, and later to other States. In this campaign mass tuberculin tests and BCG vaccinations were offered to the public. Millions of people who have been vaccinated have come forward voluntarily. The cost of the BCG programme between 1948 and 1961 was Rs.40 million. Ninety-six million persons had been tested and 34 million had been vaccinated by September 1957. By June 1959 nearly 45 million people had received the vaccination. Three-quarters of those who needed it had been vaccinated (Benjamin, 1959). At present, 170 BCG teams are working in the country, and up to the end of October 1960 the number of persons tuberculin tested was 155,199,738, of whom 54,490,871 were vaccinated with BCG vaccine. The BCG campaign in India is the biggest of its kind in the world, its aim being to protect the susceptible population in the country, which is estimated at nearly 170 million. These are mostly young people.

A study in India by the Tuberculosis Chemotherapy Centre, Madras, under the joint auspices of the Indian Council of Medical Research, the Madras State Government, the World Health Organisation and the British Medical Research Council, has shown that domiciliary treatment is as effective as institutional treatment. It would be several decades before India could afford expensive institutional care, and with present methods of treatment with oral anti-bacterial drugs and a good follow-up this may not be absolutely necessary in most cases (Editorial, *J. Ind. med. Assoc.*, 1959).

Social Factors in Tuberculosis

The national tuberculosis survey had shown that there are pockets within cities where the prevalence of the disease is as high as 5 per cent. These are generally those areas that are occupied by the poorer sections of the population, who live in crowded and insanitary conditions. There are also other factors such as malnutrition and bad social customs and habits—*e.g.* observance of "purdah" by females, early marriage and repeated pregnancies, the custom of drinking from and eating out of common utensils and smoking from the same hubble-bubble—which help the spread of infection. The disease is equally prevalent in rural areas because of increased contact of the rural population with towns, and with industry. The Rural Health Centre of the Department of Social and Preventive Medicine at Lucknow is situated 10 miles from the city. A general health survey among a population of 5,000 carried out in the area in 1958-59 showed that the most common cause of sickness found was bronchitis and tuberculosis. The general morbidity rate per 1,000 population during the past twelve months was 370 and bronchitis and tuberculosis together were responsible for 7·3 per cent. of the total. The death rate from tuberculosis in the previous year was 812 per 100,000 population, 696 per 100,000 from tuberculosis of respiratory system and 116 per 100,000 from tuberculosis of other forms. 17·6 per cent. of the crude death rate was due to pulmonary tuberculosis (Bagchi and Prasad, 1961). A random family survey carried out by medical interns in the villages of the Rural Health Centre, where in 37 families surveyed from July to September 1960, having a total

population of 240, five cases of pulmonary tuberculosis were found giving a prevalence rate of 20·8 per 1,000 of the population.

To teach social factors in disease, the fourth-year medical students (we have a five-year M.B., B.S. course) are allotted a family in the city of Lucknow having a case of tuberculosis, registered at the Kasturba Tuberculosis Clinic and Hospital of the Medical College, of which they are asked to write a medical and social history. Before they do this they are given a schedule of study (see Appendix) showing what information they must seek, and they attend a demonstration at which a case is presented in accordance with the schedule. Health visitors from the Tuberculosis Department introduce the students to the families (Prasad, 1960).

The information collected among the first 200 families studied in 1958-59 was analysed to assess the social aspects of the disease (Prasad *et al.*, 1960).

The families were selected arbitrarily from amongst the registered cases, 124 males and 76 females, in the Kasturba Tuberculosis Clinic and Hospital, King George's Medical College, Lucknow.

50 per cent. of them were Muslims, 49 per cent. were Hindus and 1 per cent. were Christians. The average size of the family was 5·78. There were 1·46 male and 0·22 female earners and 1·43 male and 2·67 female dependents. 30·5 per cent. of the families had no child, 55·0 per cent. had up to three children and 14·5 per cent. had over three children. The largest family numbered 15 members. 83·87 per cent. of the male and 11·84 per cent. of the female patients were earning, *i.e.* 56·5 per cent. of the total cases were earning.

40·5 per cent. of the families lived in congested areas, 46·5 per cent. in moderately congested, and 13 per cent. in open localities. 52·5 per cent. of the houses had damp walls, 12·5 per cent. had mud walls, 65 per cent. had no cross-ventilation, 43·5 per cent. had poor natural light and only 18·5 per cent. had electric fittings. Only 2·5 per cent. of the houses had flushed latrines and 16·5 per cent. had no latrines. 40·5 per cent. of the families were dependent on municipal stand posts for their water supply. Nearly 70 per cent. of the families were overcrowded. 63·5 per cent. of the families had not adopted proper methods for disposal of house refuse.

65·8 per cent. of the female patients (all Muslims) were observing *purdah*. 32·3 per cent. of the male and 23·2 per cent. of the female patients were married before attaining the age of 18 and 14 years respectively. 45 per cent. of the families belonged to the poor class having an income of less than Rs.75.00 p.m., 32 per cent. to lower-middle class with an income between Rs.75.00 and Rs.149.00 p.m., 20 per cent. to upper-middle class with an income between Rs.150.00 and Rs.499.00 p.m., and 3 per cent. to the rich class with an income of Rs.500.00 and over per month. 52 per cent. of the families had an unbalanced budget and 19·5 per cent. were in debt. Most of the families were spending nearly 70 per cent. of total income on food and had hardly any money for spending on health and medical care, much less on a chronic disease like tuberculosis.

22·5 per cent. of the families had one additional case of tuberculosis, 10 per cent. had two additional cases, 3.5 per cent. had three additional cases

and 0·5 per cent. had four additional cases in the family. 66 per cent. of the families took no preventive measures to check the spread of the disease. Quite a number of the patients had suffered from other infectious diseases, *viz.* typhoid (28 per cent.) and smallpox (22 per cent.). In 31·5 per cent. of the cases the probable source of tuberculous infection was from within the house, 14 per cent. from a known case of tuberculosis in the neighbourhood, 4 per cent. from contact at work. In 45·5 per cent. no clear evidence as to the source of infection could be found. 43·4 per cent. of the cases in the females and 29 per cent. in the males showed malnutrition as the precipitating cause of the disease, and in 25 per cent. of the female cases repeated pregnancies or childbirth was the precipitating cause.

The average age at the onset of disease was 29 years 3 months for male and 23 years 4 months for female patients. Nearly 80 per cent. of the patients belonged to the age group 15 to 40 years. The average duration of illness was 3 years 1 month for male and 3 years 4 months for female patients. The average period of incapacitation due to illness was 1 year 4 months for male and 1 year 5 months for female patients, that is the majority of patients were incapacitated for nearly half the duration of the illness. 34 per cent. of the patients first went to a general medical practitioner, 11·5 per cent. to *Hakims*, 5 per cent. to *Vaids*, 1 per cent. to homœopaths, 5 per cent. to quacks and 43·5 per cent. to the Kasturba T.B. Clinic and Hospital. Amongst the patients who came direct to the T.B. Clinic, 46·5 per cent. had hæmoptysis as the first symptom. Amongst the 56·5 per cent. of the patients who did not come direct to the Clinic, the average time-lag before coming to the Clinic was 11·6 months. This time-lag was much less among female patients.

66 per cent. of patients had abnormal radiographs and a positive sputum, 31 per cent. had radiological abnormalities only, 1·5 per cent. had positive sputums only, and the remaining 1·5 per cent. were diagnosed on clinical grounds. Only 46 per cent. of male cases and 26·3 per cent. of female cases were admitted in the Kasturba T.B. Hospital.

In 37·5 per cent. of the families the total income was reduced considerably because of illness, and 48·5 per cent. had accepted a loan to meet the extra expenditure. The average expenditure and average amount of debt per month of illness for poor families was Rs.15.67 and Rs.5.11, for lower-middle families it was Rs.15.49, for upper-middle families it was Rs.25.37 and Rs.11.92 and for rich families it was Rs.56.04 and nil respectively. The majority of the families had a deficit of 25 to 50 per cent. in their total income because of the illness. Out of 104 (83·9 per cent.) earning male patients, in 37 (35·6 per cent.) the income remained unaffected, in 37 (35·6 per cent.) the income was reduced by 54·3 per cent., and 30 (28·8 per cent.) patients had to give up their jobs because of incapacitation.

17·7 per cent. of the male and 56·6 per cent. of the female patients were illiterate. Only 20·2 per cent. of the male and 26·3 per cent. of the female patients had not been married. The average age at marriage for the men was 19 years 6 months and for women 15 years 8 months (the age at consummation of marriage in the females was 16 years 3 months). Child-bearing could,

therefore, start during adolescence and thus become a hazard to health. 42·3 per cent. of the total child-births were " improvident maternities."* In one case there were thirteen pregnancies.

15·3 per cent. of male and 44·7 per cent. of female patients were living on emergency subsistence or semi-starvation diets. Female patients on the whole had a poor diet compared with male patients. Diets were deficient in proteins (especially animal proteins), fats (especially animal fats), carbohydrates, vitamins (especially vitamins A and C) and minerals (especially calcium). Only 7·5 per cent. of the patients, after instructions by the Health Visitors, could improve their diet by taking milk and fruits, and all these were male patients. In 58·5 per cent. of the cases, due to the deterioration in the economic condition, the nutritive value of the diet decreased.

The cordiality of marital life remained satisfactory in over 75 per cent. of the cases. In only 7·5 per cent. of the families the cordiality of family relations was strained due to presence of the illness, and in 1·5 per cent. of the families the relations were broken. 91 per cent. of the families, therefore, had satisfactory family relations.

The study of the attitude of the patients towards the disease was based on the first reaction shown by patients on becoming aware that they were suffering from tuberculosis. The male patients exceeded the female patients in showing fear, the percentage being 40·3 and 18·4 respectively. Female patients exceeded the male patients in having a fatalistic attitude towards the disease, the percentage being 36·9 and 8·9 respectively. Superstition, hatred and guilt were more prevalent among the male patients, while apathy to the disease was more marked among the female patients.

Nine patients were helped with a small monetary grant by the Uttar Pradesh Government. Eight patients were helped by their relatives with cash or in kind. In addition eight female relatives sold their ornaments for the treatment of male patients in their families and two female patients sold ornaments for their own treatment. In two cases help was received from the public. 37·5 per cent. of the patients were taking skimmed milk from the distribution centre at the Kasturba T.B. Clinic.

Summary

1. Pulmonary tuberculosis in India since the introduction of the malaria eradication programme has become the chief cause of death. It is responsible for half a million deaths annually.

2. Reporting of vital statistics in India is not accurate and therefore mortality figures may not be reliable. Until recently morbidity estimates of the disease were also not available. In Uttar Pradesh in 1949-51, before the introduction of mass BCG vaccination, the tuberculin positivity rate was nearly 20 per cent. in the age group 0-6 years and 50 per cent. in the age group 7-14 years. The infection rate was higher in urban than in rural areas, but

* Defined by the Census Commissioner, Government of India, in 1951 as " Childbirth occurring to a mother who has already given birth to three or more children of whom one at least is alive."

the difference was not well marked. In industrial cities about 75 per cent. of the population become positive by the age of 15.

3. A sample survey to estimate the prevalence of the disease was undertaken in 1955-58 in different parts of the country. The survey was the first major attempt at a systematic assessment of the magnitude of the tuberculosis problem in India. The survey covered six zones, X-rayed 290,758 people in 6 cities, 30 towns and 151 villages. The morbidity rate revealed by this survey was 13 to 25 per 1,000 population. It also revealed that there is not much difference in the prevalence rates in urban and rural areas. The prevalence rates in older age-groups are higher than in younger age groups.

4. It is estimated that in India there are about 2·5 million open cases of tuberculosis and nearly half a million people die annually from it. The mortality rate from tuberculosis is about 150 per 100,000 of the population. Institutional facilities for tuberculosis are meagre and costly. In 1958 there were only 25,000 beds for tuberculosis. Therefore the national policy for the control of tuberculosis is to prevent tuberculosis by mass BCG vaccination (between 1951-60 nearly 150 million people had been tuberculin tested and 54 million have been vaccinated) and to provide treatment of patients in their homes from the tuberculosis clinics. It has been found that treatment of patients in their homes with anti-bacterial drugs is as effective as their treatment in hospitals and sanatoria.

5. A study of social aspects of tuberculosis was made in 200 tuberculous families in Lucknow City and its findings are given.

REFERENCES

Bagchi, S. C., and Prasad, B. G. (1961): "General health survey in a group of villages in Rural Health Centre, Sarojini Nagar, Lucknow," *J. Indian med. Ass.*, **36**, p. 348.

Benjamin, P. V., Verghese, M. C., Jesudian, K. T., and Varkey, C. E. (1939): "A tuberculosis survey in a south Indian town," *Ind. med. Gaz.*, **74**, pp. 519-526.

Benjamin, P. V. (1958): "Deadly diseases declining—Tuberculosis," *Swasth Hind*, **2**, p. 50.

Benjamin, P. V. (1959): "BCG and fight against tuberculosis in India," *Swasth Hind*, **3**, p. 126.

Editorial (1959): "Mass treatment of tuberculosis at home," *J. Indian med. Ass.*, **33**, p. 336.

Frimodt-Moller, J., Benjamin, P., and Mathew, P. (1952): "Results of mass X-ray surveys in a village population at Madanapalle," *Proceedings of the Ninth Tuberculosis Worker's Conference, Lucknow, India—February*, 1952, p. 133.

Indian Council of Medical Research, New Delhi (1959): Tuberculosis in India. A Sample Survey 1955-58.

Lal, R. B., Majumdar, S. M., and Ahmed, J. (1943): A report on tuberculosis surveys in an urban and rural area in Bengal, Government of Bengal, Public Health Department.

Mahrotra, M. L. (1960): The position of tuberculosis in the State (under publication in "The State of Health of Uttar Pradesh with particular reference to certain diseases").

Prasad, B. G. (1949): "Incidence and control of kala-azar in the eastern districts of United Provinces," *Ind. med. Gaz.*, **84**, p. 269.

Prasad, B. G. (1952): "Reporting of vital statistics in the rural areas of Uttar Pradesh, *Ind. med. Gaz.*, **87**, p. 167.

Prasad, B. G. (1960): "Family studies by students—Innovations at Lucknow," *Lancet*, October 1, 1960, p. 757.

Prasad, B. G., Jain, P. C. and Nayar, S. B. (1960): "A study of social aspects of tuberculosis in some tuberculous families in Lucknow City," *Proceedings of the Sixteenth Tuberculosis Workers' Conference*, Poona, India.

Report of the Health Survey and Development Committee (1946): Government of India, Vol. II, p. 157. Manager of Publications, Delhi.

Zimmer, H. R. (1948): "Hindu Medicine." Baltimore: The Johns Hopkins Press.

APPENDIX

SCHEDULE OF STUDY

Medico-Social Case History of Tubercular Patients

Name of the Student *Name of the Health Visitor in charge* *Hospital Registration No.*

A. Personal History

1. Name and address.
2. Age and sex.
3. Religion, caste and subcaste.
4. Occupation:
   (1) Personal occupation.
   (2) Family occupation, if any.
5. Marital status—single, married, widow or widower, divorced or remarried.
6. Educational status.
7. Habits.
8. Sleeping hours and rest.
9. Interests, hobbies, relaxations and recreations.
10. Exercises and games.
11. Routine of a typical day.
12. Present complaints in short.
13. Duration of illness.
14. Duration of incapacitation due to illness.
15. Diagnosis.
16. Findings on examination.
    (1) Clinical. (2) Pathological. (3) Radiological.
17. Basis of diagnosis and extent of disease.
18. Prognosis.

B. Past Health History

1. Chronic illnesses contracted in past—if any.
2. Other previous illnesses.
3. Childhood illnesses.

C. Family History

1. Nature of the family: (1) Rural. (2) Urban.
2. Type of family: (1) Joint (2) Unitary.
3. Patient's place in the family (Head of the family or relationship with the head of the family).
4. Family health:
   (1) Hereditary illnesses.
   (2) Previous illnesses.
   (3) Present illnesses.
5. Family composition (including the patient).

Sr.	*Name*	*Age*	*Sex*	*Educational standard** (*for 10 years and over*)	*Relation to patient*
1.					
2.					
3.					
4.					
5.					

* Educational standard: (1) Just Literate (J.L.).
(2) Middle School (M.S.).
(3) School Leaving Certificate (S.L.C.).
(4) Intermediate (Int.).
(5) Degree or Diploma (Deg. or Dip.).

6. Earning members in the family:

Under 18 yrs.		*Over 18 yrs.*		*Total*	
M.	F.	M.	F.	M.	F.

7. Dependent members in the family:

Under 18 yrs.		*Over 18 yrs.*		*Total.*	
M.	F.	M.	F.	M.	F.

8. Cordiality of family relations.
9. Social customs and habits in the family having a bearing on the disease, *e.g. purdah*, use of common utensils in eating and drinking, use of common *hukkah*, betel chewing and spitting, etc.

D. Marital History

1. Age at marriage of (1) husband (2) wife.
2. Age at consummation of marriage of (1) husband (2) wife.
3. Duration of marriage.
4. Number of living children and their ages and sex:

	Age	*Sex*
(1)		
(2)		
(3)		
(4)		
(5)		

5. Total number of—
   (1) Pregnancies.
   (2) Live-births.
   (3) Still-births.
   (4) Abortions.
   (5) No. of children died, age at death, and cause of death if known.
   (6) Improvident Maternities.*
   (7) If widowed, widower, divorced or remarried, age at the event.
   (8) The cordiality of marital relations.
   (9) If unmarried, why?

E. Economic History

1. Income of the head of the family per month.
2. Income of the patient per month—
   (1) Before illness.
   (2) At present.
3. Total income of the family per month.
4. *Per capita* income of the family per month.
5. Expenditure per month on—

	Amount Rs. nP.	*Percentage of the total expenditure*
(1) Food.		
(2) Clothing.		
(3) Housing		
(4) Education.		
(5) Health and medical care.		
(6) Ceremonies.		
(7) Other amenities.		

* Improvident maternity: childbirth occurring to a mother who has already given birth to three children, of whom one at least is alive.

6. Is the budget balanced? Yes/No.
7. If no, the amount of total indebtedness of the family and the monthly interest paid if any.
8. How much of the indebtedness is due to illness?
9. Annual saving, if any.
10. Property, if any.

	Area or No.	*Value.*
(1) Housing land.		
(2) Houses.		
(3) Agricultural property—		
(*a*) land.		
(*b*) garden.		
(*c*) cattle (cows, buffaloes, bullocks).		

11. Total expenditure on the present illness.

F. DIET (one day's usual typical diet)

	Items taken	*Calories*
(1) Morning breakfast.		
1.		
2.		
3.		
(2) Lunch.		
1.		
2.		
3.		
(3) Evening tea.		
1.		
2.		
3.		
(4) Dinner.		
1.		
2.		
3.		
(5) Night.		
1.		
2.		
3.		
	Total Calories	

1. Intervals and regularity of meals (if irregular give reasons).
2. Vegetarian or non-vegetarian and reasons if vegetarian.
3. Remarks regarding the total Calories consumed and intake of protective foods (milk and milk products, green leafy vegetables, seasonal fruits, fish, meat and eggs, etc.).

G. HOUSING (draw a rough sketch of the environment)

1. Locality (present):
   (1) Congested.
   (2) Moderately congested.
   (3) Open.
2. Type of house:
   (1) Material:
      (*a*) Roof—Thatched/Tiled/Concrete.
      (*b*) Walls—Mud/Brick/Brick with plaster.
      (*c*) Floor—Mud/Brick/Concrete.

(2) Dampness:
  (a) Absent/Present.
  (b) If present, height of dampness in the walls.

3. Number of rooms:
  (1) Living.
  (2) Sleeping.
  (3) Others.

4. Ventilation:
  (1) Ratio of the total area of the windows to the total floor area of living and sleeping rooms.
  (2) Cross-ventilation present or absent.

5. Natural lighting (adequate or inadequate).

6. Area of each sleeping room and occupants and number of rooms and occupants.

Area sq. ft.	*Occupants*			*Remarks regarding overcrowding**		
	No.	*Age*	*Sex*	*Std. I*	*Std. II*	*Std. III*
	1.					
	2.					
	3.					
	4.					
	5.					

7. Water supply: Well—Sanitary/Insanitary/Hand-pump.
  Piped—House tap/Stand post.
8. Is the house electrified? Yes/No.
9. How is the refuse disposed of?
10. Latrine:
  (1) Present or absent.
  (2) If present, number of seats and type of latrine.
  Family latrine/common latrine.

H. Present Illness in General

1. Summary of present illness.

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* Overcrowding standards: A house is deemed to be overcrowded if it fails to satisfy any of the following three standards:

I. Separation of Sex: A house is deemed to be overcrowded if any two persons, 10 years old or more, of opposite sexes not living together as husband and wife, have to sleep in the same room.

II. Number of persons according to floor area.

III. Number of persons per room.

Floor area sq. ft.	*Max. No. of persons*	*No. of rooms*	*Max. No. of persons*
110 or more	2	One	2
90 up	1½	Two	3
70 up	1	Three	5
50 up	1/2	Four	7½
Under 50	0	Five	10

A child under 1 year is not taken account of. A child of + 1 but under 10 years is reckoned as one-half.

Add two persons for each room over five.

2. Source of infection:
   (1) What the patient thinks?
   (2) What the student thinks?
3. Sources of medical aid.
4. Time lag between onset of illness and treatment, if any, and reasons for the same.
5. Measures taken, if any, to check further spread of the disease in the family.
6. Any secondary cases in the family.
7. Arrangements for the follow-up of the case.

I. Socio-Economic Problems due to Illness

1. Economic.
   How the extra expenditure on treatment effects—
   (1) Nutritive value of the diet.
   (2) Education of children.
   (3) Treatment, itself.
   (4) Family economy in general.
2. Job and rehabilitation.
   (1) Long-term leave or absence (created by the nature of illness) affecting the job.
      (*a*) Loss of pay.
      (*b*) Loss of job.
   (2) Adjustment to a new job and difficulties connected with it.
      (*a*) Loss of a job in which trained.
      (*b*) Unsuitability of the previous job due to incapacitation.
      (*c*) Difficulties in getting new job.
   (3) Inability to work and earn a livelihood.

. Psychological or Emotional Effects of the Disease

1. Hospitalisation and its effect:
   (1) How long the patient had to wait or is waiting (in months) for admission in the hospital? If admitted, total stay in the hospital.
   (2) How separation from home has affected the psychology of the patient?
   (3) How deviation from the normal routine life affects the patient?
   (4) How the fact that he is a chronic and/or stigmatic patient affects the patient?
   (5) How the disruption of the family routine and the absence of a proper home-help affects the patient (especially in the case of women patients)?
2. Disturbance in marital relations:
   (1) Prohibited sex relations and its effect.
   (2) Fear of denouncement by the spouse.
   (3) Fear of spouse being unsatisfied.
3. Attitude towards illness and effect on personality:
   (1) Fear.
   (2) Superstition.
   (3) Guilt.
   (4) Taboo and shame.
   (5) Fatalism.
   (6) Acceptance.
   (7) Revolt.
   (8) Apathy.
   (9) Hatred.
4. Worries and anxieties (financial, social, occupational, domestic, personal).

K. Family and Community
1. Inter-familial and community relationship.
2. Social and voluntary agencies working in the area.
3. Attitude towards the use of health facilities existing in the community.

L. Social Therapy and Rehabilitation
1. What should be done?
2. What can be done to provide—
   (1) Hospital or home treatment?
   (2) Financial assistance?
   (3) Food supplements?
   (4) Housing?
   (5) Vocational training?
   (6) Sheltered job?
   (7) Better family relations?
   (8) Any other assistance?

M. Conclusions:
1. Source of infection.
2. Circumstances which led to the disease (social pathology).
3. If the disease was preventable why it could not be prevented?
4. Levels of prevention recommended:
   (1) In the case of patient.
   (2) In the case of family members.
5. Likely result of the disease.
6. Is there any danger of the spread of the disease to:
   (1) Family members?
   (2) Neighbours?

N. Summary of the Case bringing out the Main Points (one page only).

Brit. J. Dis. Chest (1961) **55**, 185.

A CONTROLLED TRIAL OF CALCIUM B-PAS

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Calcium B-PAS (calcium benzamidosalicylate) was introduced in 1948 and has since been widely used in anti-tuberculous therapy in substitution for or in preference to preparations of PAS. Its capacity of preventing the emergence of drug resistance is still in dispute, and it was thought that a controlled clinical trial would be of value.

Method

Two preparations coded "A" and "B" in identical cachets were used. Each cachet contained 33·3 mg. isoniazid and either 1·25 g. sodium PAS or 1·25 g. calcium B-PAS, but which contained PAS and which B-PAS was unknown to us until the end of the trial. Patients admitted to hospital from December 1958 to June 1960 with active previously untreated pulmonary tuberculosis were allocated alternately to "A" or "B" therapy. Patients received twelve cachets daily giving a dose of 400 mg. isoniazid, plus either 15 g. sodium PAS or 15 g. calcium B-PAS. Patients so seriously ill that it seemed unjustifiable to withhold triple drug therapy with or without steroids were not admitted to the trial.

Chest radiography and culture of respiratory secretions obtained by bronchial lavage (Lees *et al.*, 1955) were carried out routinely; initially, at three months, and at six months. All patients were treated in hospital for at least three months and drug administration was carefully supervised; thereafter if cultures were negative, if cavity closure had been achieved, and if radiological progress was otherwise satisfactory, those patients with suitable backgrounds and domestic circumstances were supervised as out-patients. Before leaving hospital, patients were impressed with the importance of taking their drugs regularly, and at subsequent monthly out-patient attendances urine was tested for PAS.

Specimens of respiratory secretions were concentrated by Petroff's method (Mackie and McCartney, 1953) and inoculated on to slopes of Löwenstein-

Table 1.—Distribution of Patients by Sex and Age

Sex	*Group*	*Total*	*Distribution of patients in age groups (years)*							*Average age (yrs.)*
			0-14	*15-24*	*25-34*	*35-44*	*45-54*	*55-64*	*65-74*	*75+*	
Male	PAS	47	1	11	7	6	14	5	3	0	40·2
	B-PAS	43	0	12	4	11	9	3	3	1	39·6
Female	PAS	19	1	6	5	3	2	1	0	1	32·9
	B-PAS	23	0	10	8	2	3	0	0	0	28·0

(*Received for publication June 28, 1961.*)

TABLE 2.—CLASSIFICATION OF PATIENTS ACCORDING TO LUNG ZONE INVOLVEMENT AND NO. OF LUNG ZONES CLEARED BY SIX MONTHS

Group	Total No. of patients	No. with 6 zones involved	No. with 5 zones involved	No. with 4 zones involved	No. with 3 zones involved	No. with 2 zones involved	No. with 1 zone involved	Total No. of zones involved	Total No. of zones cleared by 6 months	% Zones cleared by 6 months
PAS	66	6	8	5	15	18	14	191	70	36·6%
B-PAS ..	66	7	2	8	9	25	15	176	71	40·3%

TABLE 4.—BACTERIOLOGICAL RESULTS

Group	Number of patients	Number culture positive at start	3 MONTHS					6 MONTHS					
			Number culture positive	Number with resistance	Resistant to isoniazid		Resistant to both isoniazid and PAS (5 μg. Isoniazid and 2 μg. PAS)	Number culture positive	Number with resistance	Resistant to isoniazid		Resistant to PAS	
					5 μg.	5 μg. and 50 μg.				5 μg.	5 μg. and 50 μg.	2 μg.	2 μg. and 100 μg.
PAS	66	56	10	2	1	—	1*	3	2	1	1	—	—
B-PAS	66	53	8	2	1*	1	—	2	2	—	1	—	1

* Converted at 6 months.

Jensen's medium. Sensitivity tests were made on Löwenstein-Jensen slopes containing the following concentrations of isoniazid and PAS: isoniazid 5 μg. and 50 μg. per ml; PAS 2 μg. and 100 μg. per ml. Organisms were reported resistant when growth was present in either concentration. Patients with organisms initially resistant to either drug were excluded from the trial. Which drug preparation contained sodium PAS and which calcium B-PAS was made known only after the results had been analysed.

Results

Withdrawals: 165 patients with organisms sensitive to isoniazid and PAS were admitted to the trial, 83 in the PAS group and 82 in the B-PAS group. 17 patients were withdrawn from the PAS group for the following reasons: lack of co-operation in treatment (6), transfer to other areas (3), death unrelated to tuberculosis or to treatment (5), coexistence of malignant disease (1), and drug allergy (2). 16 patients were withdrawn from the B-PAS group for the following reasons: lack of co-operation in treatment (5), transfer to other areas (2), death unrelated to tuberculosis or to treatment (3), coexistence of malignant disease (2), and drug allergy (4). 132 patients therefore completed the six months trial, 66 in the PAS group and 66 in the B-PAS group.

Age and Sex Distribution: Table 1 shows that the distribution of patients by sex and age is fairly similar.

Initial Weight: The average weight of men in the PAS group was 118 lb. and in the B-PAS group 122·6 lb.; the average weights of women were 107·6 lb. and 109·6 lb. respectively.

Clearing of Lung Zones: Table 2 shows that the number of lung zones initially affected by tuberculosis in each group was similar, as was also the number which had cleared by six months. The PAS group, however, had a slight excess of patients with more than two zones involved.

Table 3.—Number and Size of Cavities in Each Group at the Start, and Number closed at Six Months

Group	*No. of patients*	*No. of cavities at start*				*No. of cavities closed at 6 months*	*% cavities closed*
		Total	*2″ and more*	*1″ and more, less than 2″*	*Less than 1″*		
PAS	66	76	3	32	41	48	63·2%
B-PAS	66	73	4	22	47	49	67·1%

Cavitation: Table 3 shows the number of cavities and their distribution by size in each group at the start, and the number which had closed by six months. The number of cavities initially present in each group was approximately the same, but the PAS group had more medium-sized cavities and fewer small cavities than the B-PAS group. The number of cavities closing in each group was much the same.

Bacteriology: Table 4 shows the number of patients who had positive

cultures at the start, at three months, and at six months; and the number of patients with resistant organisms at three months and at six months. None of the patients who were bacteriologically negative at the start became positive subsequently, although X-ray response indicated that the disease had been active. At three months 10 patients in the PAS group were positive and 2 had resistant organisms; in both the resistant cases the organisms grew in the lesser concentration of isoniazid, and in one in the lesser concentration of PAS. At three months 8 patients were positive in the B-PAS group and 2 had resistant organisms; in 1 of the resistant cases the organisms grew in the lesser concentration of isoniazid and in the other in both concentrations of isoniazid. At six months 3 patients in the PAS group were positive and 2 had resistant organisms; in 1 of the resistant cases there was growth in the lesser concentration of isoniazid and in the other in both concentrations of isoniazid. At six months 2 patients in the B-PAS group were positive and both had resistant organisms; in 1 case there was growth in both concentrations of isoniazid, and in the other in both concentrations of PAS. In each group resistance had not been observed at three months in one of the 2 cases resistant at six months. In each group 1 of the 2 cases resistant at three months to the lesser concentration of isoniazid was culture negative at six months.

Discussion

In vitro, the anti-tuberculous activity of B-PAS is about 130 times less than that of PAS (Schönholzer and others, 1957). *In vivo*, PAS is liberated from B-PAS, but the blood levels are much lower than those resulting from an equal dose of PAS (Citron and Kuper, 1959). If B-PAS is dependent for its anti-tuberculous activity solely on the PAS liberated from it, it is clear that its use in conventional dosage with isoniazid would be likely to permit the emergence of bacterial resistance to the drugs employed. Although recent studies using B-PAS labelled with ^{14}C in different positions (Zeyer *et al.*, 1960) show that the intact drug is actively accumulated by tubercle bacilli and thus indicate an additional mode of action, they do not prove its clinical significance. Reports of experience with B-PAS have given rise to considerable controversy. In animal experiments using mice, Schönholzer *et al.* (1955) found B-PAS as effective as equal amounts of PAS, but Bavin and James (1953) found it much less so. In the clinical field, considering the extensive use of B-PAS over a long period, the information is surprisingly inadequate about the emergence of bacterial resistance. The clinical case against B-PAS rests almost entirely on a report by Lewis (1958) of observations on 7 cases of pulmonary tuberculosis admitted to a thoracic surgical unit. These cases had organisms initially sensitive to streptomycin, isoniazid and PAS and during part of their previous treatment calcium B-PAS had been employed in lieu of PAS for varying periods along with streptomycin or isoniazid. In 3 of the 7 cases organisms resistant to one or other of the drugs used with B-PAS were isolated and tubercle bacilli were recovered from 2 other cases after six months' treatment (part of which had included B-PAS) although sensitivity tests were not available. Because of the small number of cases involved, the highly selected nature

of the material, the fact that some of the treatment was on a domiciliary basis, and the absence of controls, it is necessary to interpret the results of this investigation with the greatest caution.

On the other hand, Gibson and Nagley investigated 204 cases of pulmonary tuberculosis treated with isoniazid and calcium B-PAS and considered that B-PAS was as satisfactory as PAS. Their conclusions have been criticised, because the duration of treatment was only two to four months and, even so, resistant organisms were found in 2 of 25 cases which had not converted. The most convincing evidence so far available about the efficacy of B-PAS has been provided by Phillips *et al.* (1957), who treated 51 cases of pulmonary tuberculosis with 12 g. B-PAS daily with either streptomycin or isoniazid for periods of from four to eighteen months, and did not detect a single case of resistance to any of the drugs used. Their paper has been criticised on the grounds that they did not state how many patients were initially sputum positive, but, in fact, all were positive (Phillips, S., personal communication).

In the present double-blind trial, 15 g. calcium B-PAS proved as effective as 15 g. sodium PAS in preventing the emergence of bacterial resistance. After three months' therapy, resistance to isoniazid had developed in 2 patients in the B-PAS group and in 2 in the PAS group. Two of these patients, 1 in each group, resistant to only the lesser concentration of isoniazid had converted by six months and follow-up has shown that continuing on the same treatment they have remained converted for a further eighteen months. After six months' therapy resistance was observed in 2 cases in the B-PAS group (in one instance to isoniazid and in the other to PAS) and in 2 cases in the PAS group (in both instances to isoniazid). In addition, there was 1 case in the PAS group still positive, but the organisms were sensitive to isoniazid and PAS. All 6 cases in which resistance developed were under hospital supervision throughout the period of their treatment, as was also the case still positive, but sensitive. The minimum concentration of isoniazid used for sensitivity testing (5 μg. per ml.) has proved by experience here to be the lowest giving consistently reliable results with the commercially prepared medium used, but some may consider it too high to detect minor but significant degrees of resistance. It is therefore worth stating that the initial sensitivity of some cases, including the 2 patients (1 in the PAS and 1 in the B-PAS group) with organisms resistant at three months and at six months was determined using additional isoniazid concentrations of 0·2 μg. per ml. and 1 μg. per ml.; in these lesser concentrations also the organisms showed no evidence of resistance.

In all cases in which resistance developed there was initially extensive cavitation; bacterial conversion is hardest to achieve in such cases and surgery may eventually be required in some. Had Lewis examined drug treatment failures in which PAS had been used, as well as failures in which B-PAS had been used, it is possible that he might have detected the development of drug resistance in the former as well as in the latter group.

The results of the present investigation indicate that calcium B-PAS in a dosage of 15 g. per day is an effective companion drug for isoniazid. They do not suggest that at this dosage level B-PAS is even marginally inferior to

PAS in its capacity to prevent the emergence of resistance to isoniazid, but it would be desirable to have these results confirmed by a sufficiently large-scale study to permit statistical evaluation. If a patient is unable to tolerate PAS the available evidence appears to warrant B-PAS an effective substitute. In the case of long-term treatment of out-patients whose disease has been brought under control, different considerations apply. Here the chief problem is not to ensure that the patient is receiving the most powerful drug combination possible, but to ensure that he is taking an effective drug combination regularly, and in this connection the unpalatability of PAS is a serious handicap. In contrast to the experience of many workers, particularly Jeker *et al.* (1959), though in conformity with that of Phillips *et al.* (1957), patients seemed to tolerate PAS as well as B-PAS, although the trial was not designed specifically to assess this feature. On the other hand, many patients find calcium B-PAS a tasteless powder, more palatable than any of the PAS preparations (Mitha, 1961). In long-term therapy aimed at preventing relapse, it is therefore both justifiable and advantageous to give B-PAS to patients who prefer it.

Summary

In a double-blind clinical trial, patients admitted to hospital with previously untreated active pulmonary tuberculosis were allocated alternately to two treatment schedules: 400 mg. isoniazid daily and either 15 g. of sodium PAS or 15 g. of calcium B-PAS daily. Patients with organisms initially resistant to either drug were withdrawn from the trial. 66 patients in the PAS group (56 initially culture positive) and 66 patients in the B-PAS group (53 initially culture positive) completed six months' therapy. After three months' therapy 10 patients in the PAS group were culture positive and in 2 cases the organisms were no longer fully sensitive to isoniazid; one of these was also no longer fully sensitive to PAS. After three months 8 patients in the B-PAS group were culture positive and in 2 cases the organisms were no longer fully sensitive to isoniazid.

After six months' therapy 3 patients in the PAS group were culture positive and in 2 cases the organisms were no longer fully sensitive to isoniazid. After six months' therapy 2 patients in the B-PAS group were culture positive; one case was resistant to isoniazid and the other to PAS.

Judging by clinical, radiological and bacteriological progress, calcium B-PAS (15 g. daily) proved as effective a companion drug for isoniazid as sodium PAS in equal dosage.

We are indebted to A. Wander Ltd. for supplying calcium B-PAS and sodium PAS in identical cachets.

REFERENCES

Bavin, E. M., and James, J. (1953): *J. Pharm. Lond.*, **5**, 849.
Citron, K. M., and Kuper, S. W. A. (1959): *Tubercle*, **40**, 443.
Gibson, M. O. J., and Nagley, M. M. (1955): *Tubercle*, **36**, 209.
Jeker, K., Lauener, H., Regli, J., and Friedrich, T. (1959): *Amer. Rev. Tuberc.*, **79**, 351.

LEES, A. W., MILLER, T. J. R., and ROBERTS, G. B. S. (1955): *Lancet*, **2**, 800.
LEWIS, D. O. (1958): *Tubercle*, **39**, 247.
MACKIE, T. J., and MCCARTNEY, J. E. (1953): "Handbook of Practical Bacteriology," 9th ed., p. 404. Edinburgh.
MITHA, K. (1961): *Tubercle*. In press.
PHILLIPS, S., LARKIN, J. C., jun., SCHLENKER, F. S., and ULRICH, E. W. (1957): *Amer. Rev. Tuberc.*, **75**, 667.
SCHÖNHOLZER, G., LAUENER, H., and HURNI, H. (1955): *Schweiz. med. Wschr.*, **85**, 222.
SCHÖNHOLZER, G., LAUENER, H., and HURNI, H. (1957): *Beitr. Klin. Tuberk.*, **117**, 456.
ZEYER, J., HURNI, H., FISCHER, R., LAUENER, E., SCHÖNHOLZER, G., and AEBI, H. (1960): *Z. Naturforsch.*, **15b**, 694.

Brit. J. Dis. Chest (1961) 55, 192.

BACTERIAL RESISTANCE IN PATIENTS WITH PULMONARY TUBERCULOSIS PRESENTING FOR TREATMENT IN GHANA

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In a survey of prevalence of bacterial resistance covering many parts of the world, but excluding Africa, Rist and Crofton (1960) showed that "6·5 per cent. of newly admitted patients who were said to have had no previous treatment had tubercle bacilli resistant to at least one of the standard drugs." The proportions varied considerably in different countries. Few estimates of the prevalence of bacterial resistance in Africa have been published, but high and rising levels among patients seen for the first time and denying previous chemotherapy for their disease have been demonstrated in East Africa by Pepys, Mitchison and Kinsley (1960) and in parts of West Africa by Bell and Brown (1960 and 1961a). Thus, it is no longer always justified to assume that patients presenting with what is believed to be previously untreated disease are fully sensitive to the major anti-tuberculosis drugs.

This paper describes the results of a survey of the prevalence of bacterial resistance in patients presenting for treatment in urban, semi-rural and rural Ghana during the first half of 1960.

Plan of Survey

The plan of the survey, together with the results of a concurrent investigation of the prevalence and pattern of resistance in patients receiving treatment, has been fully described elsewhere (Bell and Brown, 1961b). Briefly, in relation to the survey of "primary" resistance, seventeen centres in Ghana were visited. Of these, three were regional tuberculosis centres; the others were small state or mission hospitals treating tuberculous patients incidentally. The centres were scattered throughout Ghana, and were chosen deliberately as offering representative urban, semi-rural and rural conditions, and irrespective of the ease of access.

The Tuberculosis Research Unit laboratory at Accra is the only centre in Ghana with facilities for large-scale culture and sensitivity testing, and all material had to be sent there for processing. The sputum samples gathered represent a part only of the total number obtained from new patients seen at any particular centre during the period of the survey, as the forwarding of sputum depended on the availability of road or air transport to Accra on the days on which collection of sputum was possible. Sampling is believed

(*Received for publication June* 14, 1961.)

to have been representative, however, as the experiment was spread over a period of six months.

Sputum was collected from patients reporting to the centres for the first time, if they were thought on clinical grounds to have pulmonary tuberculosis and if they were believed not to have received previous drug therapy for the disease. Specimens were collected in screw-capped waxed containers and forwarded to Accra in cold boxes by road or air as quickly as possible. Any specimens from rural areas delayed *en route* to the central laboratory were refrigerated until transport was available, but no sample was delayed for more than 24 hours. All specimens reaching the laboratory were processed. Each sample was a spot specimen and the result usually of a single expectoration.

Bacteriological Methods

The method of processing sputum and of sensitivity testing has been fully described elsewhere by Brown (1959) and by Bell and Brown (1961b).

Sensitivity testing

Sputum concentrates, prepared by a trisodium phosphate technique, were inoculated on Löwenstein-Jensen slopes, two slopes being employed for each specimen. A representative sweep of each primary culture was emulsified in sterile water and seeded on plain Löwenstein-Jensen slopes, and on slopes containing anti-tuberculosis drugs in the concentrations given in Table 1 under " preliminary tests." The sensitive strain of *Mycobacterium tuberculosis* H37Rv was used as a control. The test culture was considered " sensitive " if it failed to grow on the slopes containing drugs, provided growth was obtained on the plain slopes and that growth of the H37Rv control was satisfactory. If growth of the test culture occurred on the slopes containing drugs, resistance was assumed and titration testing was undertaken using Löwenstein-Jensen slopes containing drugs in the concentrations given in Table 1 under " final titration tests." Again H37Rv was used as a control.

Table 1.—Sensitivity Testing: Concentration of Drugs in Test Media*

	Concentration of drugs in test media†								
	Preliminary tests (μg. *per ml.*)	*Final titration tests* (μg. *per ml.*)							
Streptomycin ..	10·0	2	4	8	16	32	64	128	—
PAS	1·0	0·25	0·5	1	2	4	8	16	—
Isoniazid	0·25	0·06	0·12	0·25	0·5	1	2	4	8

* Each culture was tested for resistance to cycloserine, ethionamide (1314), para-acetamidobenzaldehyde thiosemicarbazone (TB1) and viomycin. No instance of resistance to any of these drugs was demonstrated.

† Per millilitre of medium before inspissation.

Method of reading titration tests

Results of titration tests were expressed as resistance ratios, calculated by dividing the lowest concentration inhibiting growth of the test culture by the lowest concentration inhibiting growth of H37Rv control. Subcultures with resistance ratios of two or less were considered sensitive, of four partially resistant, and of eight or more fully resistant.

Catalase testing

All isoniazid resistant cultures, whether resistant to isoniazid only or also to other drugs, were tested for catalase production. To minimize admixture of resistant and sensitive colonies, only those growths occurring on slopes with the highest concentration of isoniazid were used.

Results

A total of 308 specimens of sputum was processed and the results of direct microscopy and of culture are summarised in Table 2.

Table 2.—Results of Direct Microscopy and Culture in Different Areas

Area	Number of specimens	Direct microscopy		Culture		
		Positive	Negative	Positive	Negative	Contaminated
Urban..	147	121	26	60	86	1
Semi-rural	77	39	38	31	45	1
Rural	84	50	34	34	43	7
All areas	308	210 (68%)	98 (32%)	125 (41%)	174 (56%)	9 (3%)

Of the total 210, (68 per cent.) were positive on direct microscopy, and 125 (41 per cent.) were positive on culture. The proportions positive on culture were the same in all areas.

The Extent and Pattern of Resistance

The extent and pattern of resistance are summarised in Table 3.

In all, 29 cultures (23 per cent.) were resistant to one or more drugs. Of these, 20 were resistant to one drug, 7 to two drugs, and 2 to three drugs—representing 16·0, 5·6 and 1·6 per cent. respectively of all cultures, and 69, 24 and 7 per cent. respectively of all resistant cultures.

Of the 20 resistant to one drug, 14 (70 per cent.) were resistant to isoniazid, 4 (20 per cent.) to streptomycin and 2 (10 per cent.) to PAS. Of the 7 resistant to two drugs, 5 (71 per cent.) were resistant to streptomycin and isoniazid, and 2 (29 per cent.) to PAS and isoniazid. There were no cases resistant to streptomycin and PAS.

The proportions resistant to one or more drugs were much the same in all

TABLE 3.—EXTENT AND PATTERN OF RESISTANCE IN DIFFERENT AREA

	Area							
	Urban		*Semi-rural*		*Rural*		*All areas combined*	
	No.	%	*No.*	%	*No.*	%	*No.*	%
Sensitive to all drugs	46		23		27		96	77
*Resistant to one or more drugs	14	23	8	26	7	26	29	23
† Resistant to one drug	11		5		4		20	69
streptomycin	2		1		1		4	
PAS	1		0		1		2	
isoniazid	8		4		2		14	
† Resistant to two drugs	2		3		2		7	24
streptomycin/PAS	0		0		0		0	
streptomycin/isoniazid ..	2		1		2		5	
PAS/isoniazid	0		2		0		2	
†Resistant to three drugs	1		0		1		2	7
‡ Resistant to each in total								
streptomycin	5	28	2	18	4	36	11	28
PAS	2	11	2	18	2	18	6	15
isoniazid	11	61	7	64	5	45	23	58

* Percentages are of total positive cultures in each area.
† Percentages are of total resistant cultures.
‡ Percentages are of total incidence of resistance to each drug in particular areas.

areas. Resistance to one drug was commoner in the urban areas. Isoniazid resistance accounted for 18 per cent., streptomycin for 9 per cent. and PAS for 5 per cent. of all cultures, and for 58, 28 and 15 per cent. respectively of all resistances. Isoniazid resistance was most common in the semi-rural and urban areas, and streptomycin resistance was most common in the rural and urban areas.

Resistant Ratios

Resistance ratios in respect of streptomycin, PAS and isoniazid resistant cultures are given graphically in Fig. 1.

Of the 11 cultures resistant to streptomycin, 7 (64 per cent.) were fully resistant; of the 6 cultures resistant to PAS, 3 (50 per cent.) were fully resistant; of the 23 resistant to isoniazid, 22 (96 per cent.) were fully resistant, and 20 cultures had resistance ratios of 16 or over.

Catalase Tests

The results of catalase testing of isoniazid resistant cultures are related graphically to resistance ratios in Fig. 2.

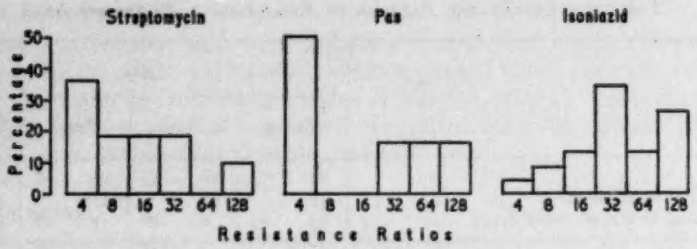

FIG. 1.

Of the 23 isoniazid resistant cultures tested, 12 (52 per cent.) were catalase negative. Failure to produce catalase was demonstrated only in those cultures with resistant ratios over 8, and in 55 per cent. of the 22 cultures considered fully resistant. All cultures with the highest resistant ratio (128) were catalase negative.

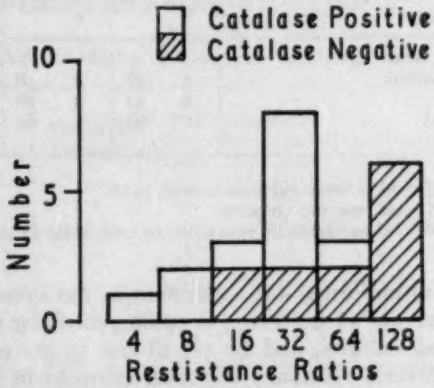

FIG. 2.

RESISTANCE RELATED TO AGE AND SEX

The differences between the proportions resistant to one or more drugs in the various areas are not material, and area results have been combined in relating resistance to age and sex and other factors. The relationship between age and sex and resistance is summarised in Table 4.

Taking all ages combined, 23·7 per cent. of the 76 male cultures and 22·4 per cent. of the 49 female cultures were resistant to one or more drugs; the difference is insignificant. Nor is the sex difference material in patients under 35 (male 19·5 per cent., female 18·2 per cent.) nor in those over 45 (male 28·6 per cent., female 33·3 per cent.). When the sexes are combined, resistance was higher in patients over 35 than in those under 35 (30·0 per cent. and 18·7 per cent. respectively)—but the difference does not attain statistical significance with the small numbers in the groups ($0{\cdot}3 > P > 0{\cdot}2$).

TABLE 4.—RESISTANCE RELATED TO SEX AND AGE

	15-24		25-34		35-44		45 and over	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
Number cultures ..	13	12	28	22	12	8	23	7
Number resistant ..	4	1	4	5	4	3	6	2
Per cent. resistant ..	31	8	14	23	33	38	26	29

RESISTANCE RELATED TO TYPE AND EXTENT OF DISEASE ON DIAGNOSTIC RADIOGRAPHS

Resistant and sensitive cultures were related to the type and extent of disease on diagnostic radiographs exposed at the time of sputum collection. Radiographs were classified as showing acute pneumonic, subacute, subacute/acute (subacute with recent acute spread), or chronic disease; a note was made of whether disease was unilateral or bilateral, and an estimate of the number of lung zones involved was recorded. Films were available in respect of 88 sensitive and 27 resistant cultures, but the one case of chronic disease was excluded from the analysis which deals therefore with 114 (88 sensitive and 26 resistant) patients. Cavities were classed as tension, thickwalled or soft-walled (areas of breakdown in association with acute exudative shadowing) and all visible cavities on each radiograph are included in the analysis of cavity type. As to size, cavities were classed as less than 2 cm., 2-4 cm. and over 4 cm., and the analysis deals only with the largest cavity visible on each radiograph. The results of the correlation of cultures with the type and extent of disease and of the type and extent of cavitation are summarised in Tables 5 and 6.

Type and Extent of Disease.—Twice as many in the subacute acute group as in the acute pneumonic or subacute groups were excreting resistant bacilli, but the individual differences could well be due to chance variation. The differences are not significant ($0{\cdot}7>P>0{\cdot}5$). A higher proportion with bilateral disease were excreting resistant bacilli, but when the extent of the disease is considered in terms of the number of zones involved, the differences are not material.

TABLE 5.—RESISTANCE RELATED TO TYPE AND EXTENT OF DISEASE ON DIAGNOSTIC RADIOGRAPHS

Cultures	*Type of disease*			*Extent of disease*						
	Acute pneumonic	*Subacute*	*Subacute acute*	*Unilateral*	*Bilateral*	*Radiological zones*				
						2	3	4	5	6
Number ..	96	9	9	13	101	7	17	31	27	32
Number resistant	20	2	4	2	24	0	5	9	4	8
Per cent. resistant	(21)	(22)	(44)	(15)	(24)	(0)	(29)	(29)	(15)	(25)

TABLE 6.—RESISTANCE RELATED TO TYPE AND SIZE OF CAVITIES ON DIAGNOSTIC RADIOGRAPHS

	Type of cavity			*No cavity*	*Size of cavity*		
	Tension	*Thickwalled*	*Softwalled*		*<2 cm.*	*2-4 cm.*	*>4 cm.*
Number	77	18	42	8	12	36	58
Number sensitive	57	12	35	7	9	29	43
Number resistant	20	6	7	1	3	7	15
Per cent. resistant	(26)	(33)	(17)	(13)	(25)	(19)	(26)

Type and Size of Cavities.—Resistant cultures were obtained from 33 per cent. of the 18 with thickwalled cavities, from 26 per cent. of the 77 with tension cavities, and from 17 per cent. of the 42 with softwalled cavities. There is the suggestion therefore that those patients presenting with thickwalled cavities are more likely to be excreting resistant bacilli than those with tension or particularly with softwalled cavities. The differences between those excreting sensitive or resistant cultures do not attain statistical significance, however ($0{\cdot}5>P>0{\cdot}3$), nor is the difference between the thickwalled and softwalled categories significant ($0{\cdot}3>P>0{\cdot}2$). Only one (13 per cent.) of the 8 patients with no obvious cavitation was excreting resistant bacilli against 25 (24 per cent.) of the 106 patients with cavities. Of the 48 whose largest cavities were under 4 cm. in size, 10 (21 per cent.) were excreting resistant bacilli; of the 58 whose largest cavities were over 4 cm. in size, 15 (26 per cent.) were resistant. Thus there is the suggestion that patients reporting with large cavities are more likely to be excreting resistant bacilli and that resistance is least likely in those who have no cavities. Among those with cavitating disease, however, the difference in respect of size is not significant ($0{\cdot}8>P>0{\cdot}7$).

Comparing single and multiple cavitation, 30 per cent. of the 27 with single cavities against 22 per cent. of the 79 with multiple cavities were excreting resistant bacilli; the difference is not significant ($0{\cdot}7>P>0{\cdot}5$).

Discussion

Because of shortage of field staff at the time the survey was undertaken, it was not possible to investigate contacts, nor was it possible fully to investigate denials of previous chemotherapy. Apart from the important epidemiological issues raised by true " primary " resistance—particularly to catalase negative isoniazid resistance—the question of whether all specimens of sputum processed related to patients who had not indeed received previous chemotherapy is largely irrelevant to this study. This was to determine the prevalence and pattern of resistance in patients reporting to diagnostic clinics apparently for the first time, who cannot be made to admit to previous treatment, and who might be assumed therefore to be sensitive to the major drugs. In most parts of West Africa, and indeed over the great part of tropical Africa, the practical problem rests in assessing how treatment can be planned against

a background of high " initial " resistance; of the need to use chemotherapy in the definitive sense, and to rely usually on the oral administration of combinations of isoniazid and PAS to ambulant outpatients; and of laboratory facilities that are scanty at best.

This survey has shown that in all parts of Ghana there is a high prevalence of initial resistance not only to one drug, but to two or three drugs in some 13 per cent. of culture positive patients (1·6 per cent. to three drugs). The high prevalence of isoniazid resistance is particularly disturbing, and if even a proportion are instances of true primary isoniazid resistance, it constitutes an argument against pressure for the use of isoniazid alone in tropical Africa and in other under-developed parts of the world.

Summary

1. A survey of the prevalence and pattern of bacterial resistance in tuberculous patients believed to have had no specific drug treatment for their disease has been undertaken in Ghana.

2. Resistance was assessed in terms of minimum inhibitory concentrations and calculated resistance ratios, and also in terms of arbitrary levels of partial and full resistance.

3. Twenty-three per cent. were resistant to one or more drugs—the great majority " fully resistant."

4. Resistance to one drug accounted for 16·0 per cent., to two drugs for 5·6 per cent., and to three drugs for almost 1·6 per cent. of all cultures, and respectively for 69, 24 and 7 per cent. of all resistances.

5. Resistance to isoniazid accounted for 58 per cent. of total resistance; 52 per cent. of isoniazid resistant cultures were catalase negative.

6. There was no material difference in prevalence in urban, semi-rural and rural Ghana; differences in prevalence between the sexes and in various age groups were not significant; it was not shown that resistance could be inferred from the appearance of the diagnostic radiograph.

REFERENCES

Bell, W. J., and Brown, P. P. (1960): *Tubercle* (*Lond.*), **41**, 247.
Bell, W. J., and Brown, P. P. (1961a): *W. Afr. med. J.*, N.S. **10**, 140.
Bell, W. J., and Brown, P. P. (1961b): In preparation.
Brown, P. P. (1959): *W. Afr. med. J.*, N.S. **8**, 244.
Fox, W., Wiener, A., Mitchison, D. A., Selkon, I. B., and Sutherland, I. (1957): *Tubercle* (*Lond.*), **38**, 71.
Pepys, J., Mitchison, D. A., and Kinsley, B. J. (1960): *Tubercle* (*Lond.*), **41**, 32.
Rist, N., and Crofton, J. (1960): *Bull. Un. int. Tuberc.*, **30**, 1, 2.

Brit. J. Dis. Chest (1961) 55, 200.

CLINICAL FINDINGS IN A MASS X-RAY CAMPAIGN

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Introduction

About 1,700 adults over the age of 15 were seen at the South Chest Clinic, one of the four clinics in Liverpool, during the Mass X-ray Campaign held between February 28 and March 21, 1959. First came those who had volunteered to help and who had their chests X-rayed before the start, then the 1,647 who were reported by the Regional Hospital Board at the end of April and in the joint report from Professor Semple and others (1960), and finally a diminishing tail of stragglers who had not kept their original appointments.

All these people were called to the clinic because their original miniature X-ray and the larger film were thought to have shown an abnormal shadow. Patients whose films showed cardiac abnormalities alone and patients already under the care of the clinic were not included in the series.

The cases were seen by the three physicians on the Chest Clinic staff and a colleague gave us some sessions during the peak period.

Findings

1. *Classification.*—Table 1 shows the abnormalities discovered. These are subdivided into three groups. Group A were mainly those who were well and who could be reassured. They did not need to be seen at the clinic more than one month after their first attendance because neither prolonged observation nor investigation was necessary. Usually this was because they had no active disease or were suffering from a condition already known to their doctors. Group "A" also included people who had an abnormality not needing treatment at the time and who could be watched by their own doctor for symptoms which might necessitate treatment later. The group also included a few patients at the other extreme; those who were too old or frail to tolerate further investigation.

Group B consisted of those patients who needed to be seen again after one month but not after one year. They needed more prolonged observation, more detailed investigation, and perhaps some advice on the management of their disabilities.

Group C contained those patients with active disease who needed observation for more than one year, who had a major operation because of the (discovered) abnormality, or who died as a result of that abnormality.

2. *Tuberculosis.* As in the Glasgow and the Edinburgh campaigns reported by Sir Kenneth Cowan and others (1958) and by Doctor Seiler and others (1958) respectively, one of the chief objects of this campaign was to attempt to eradicate as much tuberculosis as possible. A synopsis of the outcome in the group initially diagnosed is shown in Table 2.

(*Received for publication May* 31, 1961.)

TABLE I

Diagnosis	*Total*	*A One month*	*B One month to one year*	*C One year or operation or death*
I. Tuberculosis initially notified (Table 2)	370	—	—	370
II. Tuberculosis later notified (Table 3) ..	57	—	—	57
III. Tuberculosis healed	487	231	172	84
IV. Carcinoma: Malignant neoplasm (Table 4) ..	47	4	3	40
V. Secondary neoplasm	2	1	—	1
VI. Acute inflammation	152	83	69	—
VII. Fibrosis	132	64	44	24
VIII. Bronchiectasis	80	39	30	11
IX. Bronchitis	76	53	17	6
X. " Clear "	61	58	3	—
XI. Pleural thickening	48	33	6	9
XII. Cardiovascular	39	33	4	2
XIII. Cyst	17	5	4	8
XIV. Retrosternal thyroid	13	12	1	—
XV. Other thyroid abnormality	6	5	1	—
XVI. Bony abnormality	35	30	5	—
XVII. Benign tumour (Table 5)	18	7	2	9
XVIII. Diaphragmatic hernia (Table 6) ..	11	4	3	4
XIX. Eventration of diaphragm	3	2	—	1
XX. Other diaphragmatic abnormality ..	3	—	—	3
XXI. Pneumoconiosis (Table 7)	11	4	2	5
XXII. Mastectomy and irradiation fibrosis ..	10	9	1	—
XXIII. Sarcoidosis (Table 8)	6	1	1	4
XXIV. Soft tissues	4	2	1	1
XXV. Effusion	2	—	1	1
XXVI. Calcified glands	2	2	—	—
XXVII. Spontaneous pneumothorax	1	—	—	1
XXVIII. Liver abnormality	1	—	—	1
	1,694	682	370	642

Men 874, women 818.

One patient sent in to Sanatorium had tubercle bacilli in his sputum, but he also had a bronchial carcinoma from which he died. He was the one exception to the rule that only one diagnosis had been given in each case. Where there were two possible diagnoses, that which was most likely to have brought the patient to the clinic or kept him under observation has been given.

The 57 patients who shook our complacency were being kept under observation for presumed " inactive " tuberculosis, but a specimen of sputum or a laryngeal swab was eventually reported to have grown tubercle bacilli on culture. Other cases showed clinical and/or radiological deterioration. Of the 34 men, 14 had a positive sputum as had 6 of the 23 women. Further details are shown in Table 3.

The section " Healed Pulmonary Tuberculosis " includes calcified primary lesions, and other lesions which had healed leaving calcification and perhaps

a little fibrosis. Fibrosis alone and pleural thickening alone are noted separately; although a number of these people appear in groups B and C this often simply meant that about a year later they were recalled for another X-ray to confirm that the lesions had not changed.

TABLE 2.—TUBERCULOSIS INITIALLY NOTIFIED

Men	215
Women	155
Total	370
Active	317
Quiescent	63
Sent to hospital	105
Bed rest and chemotherapy at home	66
Chemotherapy: remained at work	109
Chemotherapy: housework	39

TABLE 3.—DELAYED TUBERCULOSIS

57 Patients (34 men, 23 women)

	Age under 40	*40-50*	*50-60*	*60-70*	*Over 70*
Men	5	5	12	8	4
Women	6	6	7	2	2

	Men	*Women*
Symptoms present in	25	12
Tubercle bacilli present in	14	6
Past history relevant in	16	6
Family history relevant in	1	1

OTHER CONDITIONS

Table 4 gives some idea of what happened to the patients believed or proved to have primary malignant pulmonary neoplasms. It is quite possible that there were even more deaths among section (*a*), those who were unfit for surgery, and (*b*), those who refused investigation or surgery, for many of these passed out of the care of the clinic, but the patients in section (*c*) are among those described in Mr. Waddington's series (1960) and all of these have been kept under observation.

Of the 2 cases classified under secondary neoplasm the first, a woman of 71, had had a mastectomy for primary carcinoma of breast, the second was a man of 78 with a recurrence of a primary carcinoma of bronchus.

The campaign arrived close on the heels of an influenza epidemic and with a burst of respiratory infections. There were therefore many people with "unresolved pneumonia" and "catarrhal shadows" who were kept under observation until the signs and symptoms had gone. In most cases this occurred within four weeks and in all within a few months.

Included in the group with bronchiectasis was one case of a cystic lobe.

No separate group of Emphysema is noted as in the Glasgow report. Cases with signs and symptoms of emphysema are included under associated conditions such as bronchitis where the diagnosis was made clinically. In a few cases the outstanding feature was bullæ.

TABLE 4.—MALIGNANT NEOPLASMS

47 Patients (39 men, 8 women)

(*a*) Unfit for surgery and/or investigation—16 patients.
15 men (10 known to be dead), 1 woman.
Bronchoscopy performed in 5 men and 1 woman.
Unfit for bronchoscopy 10 men.
Age 40-50 (1), 50-60 (2), 60-70 (6), over 70 (7).

(*b*) Refused investigation and/or surgery—8 patients.
6 men (2 known to be dead), 2 women.
Age 50-60 (2), 60-70 (2), over 70 (4).

(*c*) Operations—23 patients.
18 men (5 known to be dead), 5 women.
Age under 40 (1), 40-50 (6), 50-60 (11), 60-70 (5).

Of the 13 cases with a retrosternal thyroid there were 10 women in Group A aged respectively 40, 55, 61, 62, 62, 64, 69, 75, 75, 85. A 59-year-old woman was recalled after six months for a further X-ray. The two men, both in group A, were aged 60 and 69. All were symptom free.

In addition there were two women aged 60 and 63 and one man aged 33 with large thyroid shadows, and three women with calcification of the thyroid, aged 66, 69 and 72. All were in group A except one of the women with calcification who was recalled once after three months.

The bony abnormalities included congenital and acquired skeletal deformities and defects, and the results of injury and operations. The only skeletal abnormality needing an operation was a chondroma which became painful: this is included under " benign tumour."

TABLE 5.—SIMPLE OR BENIGN TUMOUR

18 Patients (8 men, 10 women)

MEN		WOMEN	
Age	*Comment*	*Age*	*Comment*
54 C	Tumour diaphragm. Known 1940.	78 A	Too old for investigation.
41 C	Chondroma + symptoms. Op. 1959.	53 C	? Pericardial lipoma.
58 B	Lipoma.	71 A	Lipoma.
54 C	Hamartoma Op. 9.11.60.	62 A	Adenoma of bronchus. Known 1949.
60 A	„ known 1958.	66 C	Hamartoma. Known 1950.
56 C	? „ June, 1960. I.S.Q.	38 C	Ganglio neuroma. Op. April, 1960.
77 B	Extra thoracic nodule. March, 1960. I.S.Q.	66 A	Tumour. Known 1953.
57 A	Chrondroma (tiny). No symptoms.	56 A	? Lipoma. No symptoms.
		52 C	Neurilemmoma. Op. April, 1959.
		57 C	Hamartoma. Op. June, 1959.

The group of simple tumours set out in Table 5 includes hamartomata, some of which were removed because previous X-rays were not available to help to exclude a neoplasm.

In eleven patients a diaphragmatic hernia was found, in two of these an operation was recommended. Three patients with eventration were found, and three with other diaphragmatic abnormalities (Table 6).

TABLE 6.—DIAPHRAGMATIC HERNIA
11 Patients (4 men, 7 women)

Men		Women	
Age	*Comment*	*Age*	*Comment*
80 A	Frail.	73 A	Already known.
48 C	Traumatic. Known since 1956.	58 B	Under c/o own doctor.
67 B	Respiratory symptoms.	77 C	Severe. Medical treatment.
70 A	Investigation refused.	77 A	Frail. Rheumatoid arthritis.
		69 B	Mild symptoms.
		52 C	Operation advised and refused.
		58 C	Operation satisfactory.

The eleven men shown in Table 7 had pneumoconiosis. One failed to attend for examination, one was already under the supervision of the Pneumoconiosis Board; of the others, five had been stonemasons, two had drilled rock making sewers, one had been a coal miner, and one had spent twenty-five years in the disposal of locomotive fire-box ash.

Of the ten women who had been treated by combined mastectomy and irradiation, nine needed only to be seen once for the diagnosis to be confirmed and one was seen again after an interval of four months: none had symptoms.

TABLE 7.—PNEUMOCONIOSIS (SILICOSIS)
11 Men

(A)		(B)		(C)	
Age	*Remarks*	*Age*	*Remarks*	*Age*	*Remarks*
78	Ex stonemason. Known. No claim.	63	Known to Board.	44	30 years stonemason.
78	Miner until 1949.	63	25 years coal ash disposal.	67	Rock tunneller, claimed.
77	Ex stonemason.			57	33 years stonemason.
56	Did not attend.			75	Ex stonemason. No claim.
				55	Rock tunneller 25 years.

None of the six young people with sarcoidosis shown in Table 8 was seriously ill. The three men were fit, the women all had some symptoms, and one was sufficiently ill to need repeated admission to hospital for the treatment of recurrent infections associated with her bronchiectasis. She and one of the other women have each had a normal pregnancy and delivery since 1959.

There were only two effusions unassociated with other lesions. One was a small encysted effusion known to have been present fifteen years earlier. The other was a cholestrol effusion in a man of 65.

The spontaneous pneumothorax occurred in a man of 27. It absorbed

without special measures and did not recur during the year he was kept under observation.

TABLE 8.—SARCOIDOSIS

6 Patients (3 men, 3 women)

MEN		WOMEN	
Age	*Remarks*	*Age*	*Remarks*
26 C	Symptomless.	20 C	Marked symptoms and bronchiectasis.
27 B	Symptomless.	29 C	Mild symptoms.
27 A	Symptomless and would not attend again.	41 C	Mild symptoms.

Discussion

As well as the deflection of thirty-one X-ray units from their normal work in England, Scotland and Wales, the expense and the dislocation of routine care due to the campaign as a whole, these figures represent 1,694 people who spent days and nights of anxiety from the time they were recalled for a further X-ray at least until they had been seen at the clinic. The advocates of the Mass Radiography Campaign can claim that a significant amount of relatively symptomless disease which would later have menaced the individual and, in the case of tuberculosis, his family was found and treated. Diagnoses helpful to the patient and his doctor were made in less serious conditions and saved time and investigation later when perhaps the patient would have been less fit to stand it. Patients who had soundly healed disease, or with those conditions already receiving adequate care, or clear chest X-rays, were almost uniformly grateful to have had the opportunity of another opinion, and many asked about the advisability of further "check-ups." Each one seen has at least one X-ray available at the clinic if trouble arises in the next few years, and those who were not recalled have the assurance that there was little amiss with their chests in March 1959. The danger here is that symptoms arising later may be ignored through a false sense of security.

Is it possible to obtain these advantages in future without all the upset; to have a knowledge of everyone's "usual" radiological condition so that variations from his normal can be quickly detected?

To avoid anxiety from transient shadows it should be safe to wait for three weeks after the onset of a simple upper respiratory infection before taking a chest X-ray. On the other hand, an X-ray is always advisable where respiratory symptoms are severe or persist for longer than three weeks.

A chest X-ray is necessary for everyone with a productive cough persisting for more than three weeks and this must be combined with examination of the sputum. Persistent signs and symptoms of respiratory disease constitute an absolute indication for X-ray.

It is becoming increasingly common, though still not invariable, to X-ray the chest of patients with associated conditions which make them more liable to tuberculosis. This should be done in everyone with a debilitating disease,

especially those with diabetes, rheumatoid arthritis, anæmia, gastro-intestinal disease, and those having major surgery especially on the alimentary canal. Even those who had had surgery for an ischiorectal abscess had sometimes escaped without a chest X-ray. Mental subnormality and inadequate living conditions should also suggest the possibility of pulmonary tuberculosis.

Patients being treated with corticosteroids need special care and those with congenital abnormalities elsewhere might well have a chest X-ray in the absence of respiratory symptoms to determine the appearances normal for them, so that any change due to disease developing later can be seen.

There are others for whom watchful care is necessary. They are those giving a history of a previous respiratory illness, or those known to have had a previously abnormal X-ray, or found to have been in close contact with a case of tuberculosis. In the latter group a single X-ray immediately after contact is insufficient to exclude infection, and a further X-ray should be taken after six months to one year.

Though less essential there are other groups where a chest X-ray is advisable. Some occupations carry a risk to the individual, for example medical, nursing, laboratory, domestic staff and students exposed to tubercle bacilli, and those breathing dust-laden air; these should be X-rayed for their own sake. Those in contact with children under 15 or those handling food should be X-rayed to ensure others are not being exposed to infection. While school teachers are now X-rayed on appointment, several school caretakers and canteen staff were found who had never been X-rayed.

Should all smokers over 40 have routine X-rays to detect early carcinoma? Should younger women and older men be similarly examined to detect latent tuberculosis? Should a chest X-ray be part of the examination of every child about to leave school and of every routine medical examination in adults? To avoid undue irradiation in pregnancy, should girls be encouraged to go for an X-ray before marriage?

Practical considerations, especially the shortage of radiographers, may make such practices impossible at present.

Conclusion

A mass X-ray campaign has disadvantages as well as the obvious advantages.

Consideration should be given to obtaining effective results by routine procedures. The discovery of disease in its early stages should be possible by paying yet more attention to the X-raying of selected groups.

It is valuable for every adult to have had a chest X-ray; for the individual as well as his doctor to know the result of this and to know for future reference where that X-ray can be obtained.

Summary

1. The 1959 Mass X-ray Campaign enabled one clinic to discover 427 cases of tuberculosis needing at least close observation, 47 cases of malignant neoplasm and 215 significant abnormalities needing surgery, more than a year of medical supervision, or which proved fatal.

2. 370 patients needed treatment and investigation taking less than a year but more than one month.

3. 682 people had no need to be seen again at the clinic one month after their first visit.

4. The various abnormalities found are described, and whether it was normal or abnormal, the value of a previous chest X-ray for comparison should future trouble arise is stressed.

I am grateful to Doctor Crawley and Doctor Poniedel for access to their patients' X-rays and case notes, to Doctor Whyte for his help with seeing patients when the campaign reached its peak, and to Doctor Lloyd Hughes for his interest.

REFERENCES

COWAN, SIR KENNETH, HOME, W. A., GEDDES, J. G., TAIT, A. W., and MACGREGOR, I. M. (1958): Report on Glasgow X-ray Campaign against Tuberculosis 1957.

SEILER, H. E., WELSTEAD, A. G., and WILLIAMSON, I. (1958): Report on Edinburgh X-ray Campaign 1958, *Tubercle, (Lond.)*, **39**, 339.

SEMPLE, A. B., and LLOYD HUGHES, T. (1960): Liverpool Mass Radiography Campaign, 1959.

WADDINGTON, J. K. B. (1960): "Surgical aspects of the Mass X-ray Campaign, Liverpool, 1959," *Med. Offr.*, **104**, 293.

Brit. J. Dis. Chest (1961) 55, 208.

MECAMYLAMINE AND CHLOROTHIAZIDE IN THE TREATMENT OF HYPERTENSION IN OUT-PATIENTS

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This is an account of the prolonged use of mecamylamine and chlorothiazide in 30 patients with hypertension. The indications for treatment were persistent elevation of the diastolic pressure to (or above) 110 mm. Hg, evidence of cardiac overload (congestive heart failure in 7, left ventricular failure in 16, electrocardiographic signs of left ventricular hypertrophy in 29, and radiological signs of left or generalised cardiac enlargement in 15), and hypertensive retinopathy of varying severity (24 cases).

The majority of the patients were admitted to hospital for the first two weeks of treatment and were followed up as outpatients at intervals of one to three months. Examination was done three to four hours after the morning dose of mecamylamine. The blood pressure was taken twice lying down and twice standing up. The means of these readings in two successive outpatients' visits are shown in the tables before hypotensive therapy (initial) and at the time of the last assessment (final).

The individual dose of mecamylamine (Tables 1 and 2) was divided into two halves given in the morning and in the evening respectively, but occasionally the latter was the larger of the two. By " initial " dose is meant the amount at which the blood pressure appeared to be controlled after readjustments in the first three to four weeks; the " final " dose indicates the amount given at the time of the last examination. Chlorothiazide was given in all cases except two, which were treated with mecamylamine alone throughout. The daily dose of chlorothiazide was 0·5 g. in 24 patients and 1·0 g. in four.

Results

In 11 patients (Table 1) treated with mecamylamine alone for an average period of 21 months, the blood pressure fell from $\frac{207\ (170\text{-}230)}{115\ (100\text{-}130)}$ mm. Hg to $\frac{181\ (150\text{-}210)}{102\ (90\text{-}115)}$ mm. Hg. The daily dose of mecamylamine, before chlorothiazide was started, ranged between 10 and 80 mg. (mean 36 mg.). With addition of the chlorothiazide in cases 3 to 11 (Table 1) reduction of the amount of mecamylamine was always possible without loss of hypotensive effect, so that the mean " final " dose was 47 per cent. lower than that before the administration of chlorothiazide.

* Work done during the tenure of a British Council Scholarship (1958-59) from Athens. Present address: Royal Victoria Hospital, Montreal, Canada.

(*Received for publication May* 20, 1961.)

TABLE 1.—RESULTS OF TREATMENT IN PATIENTS RECEIVING MECAMYLAMINE BEFORE AND AFTER THE ADDITION OF CHLOROTHIAZIDE

No.	Sex	Age	Diagnosis	*Before Chlorothiazide*					*After Chlorothiazide*				
				Mecamylamine dose		*Blood pressure*		*Duration in months*	*Mecamylamine dose*		*Blood pressure*		*Duration in months*
				Initial	*Final*	*Initial*	*Final*		*Initial*	*Final*	*Initial*	*Final*	
1	F	59	EH	10	20	225/110	170/95	33					
2	M	57	RH	35	35	200/110	190/100	33					
3	F	50	EH, MS	10	35	220/130	175/100	24	10	10	175/100	160/90	12
4	F	58	EH, MS, AS	20	27·5	230/130	180/90	18	10*	10	180/90	180/90	16
5	M	46	EH	30	35	220/120	170/105	18	20	25	170/105	175/105	13
6	M	23	EH	20	30	170/110	150/100	18	10	15	150/100	160/100	11
7	M	50	EH	50	55	200/110	180/100	24	40	40	180/100	170/100	11
8	F	59	EH	10	80	220/120	195/100	24	5*	25	195/100	195/100	15
9	F	41	EH	35	50	190/110	180/110	22	15	20	180/110	175/110	14
10	M	65	EH	5	10	200/110	210/110	4	10	15	210/110	220/120	7
11	M	64	EH	15	20	200/110	190/110	6	10	15	190/110	185/110	12

Abbreviations: EH: essential hypertension. MS: mitral stenosis.
RH: renal hypertension. AS: aortic stenosis.
MH: malignant hypertension. CAA: coarctation of abdominal aorta.

* Patients given 1 gm. of chlorothiazide.

Both drugs were administered from the beginning in the patients shown in Table 2, producing a fall of pressure from $\frac{211\ (180\text{-}240)}{122\ (100\text{-}140)}$ mm. Hg to $\frac{184\ (150\text{-}230)}{108\ (80\text{-}140)}$ mm. Hg. The average final dose of mecamylamine in these patients was of the same order as in patients 3 to 11 of Table 1 during the period of combined treatment: it ranged between 5 and 35 mg. daily.

Dyspnœa on effort was significantly improved in 11 of 16 patients and paroxysmal nocturnal dyspnœa disappeared completely in the 4 in whom it was present. Five patients were relieved from congestive heart failure and two were

TABLE 2.—RESULTS IN PATIENTS RECEIVING BOTH MECAMYLAMINE AND CHLOROTHIAZIDE

No.	*Sex*	*Age*	*Diagnosis*	*Mecamylamine dose*		*Blood pressure*		*Duration in months*
				Initial	*Final*	*Initial*	*Final*	
1	M	68	EH	5	10	200/110	175/90	13
2	M	57	MH	10	25	215/140	185/110	13
3	F	52	MH	10	20	240/135	190/115	12
4	F	47	EH	10	15	190/110	170/100	14*
5	F	62	EH	10	10	220/140	170/95	5
6	M	59	EH	5	30	240/110	205/100	11
7	M	65	EH	10	15	200/110	150/80	13
8	M	46	EH	25	20	200/130	145/90	15
9	F	34	EH	5	10	190/105	160/90	13
10	M	57	EH	10	20	200/120	180/110	10
11	M	38	EH	5	15	210/120	200/110	11
12	M	51	MH	5	25	220/140	170/100	16
13	M	53	EH	5	30	180/120	160/100	14*
14	F	32	CAA	5	35	225/120	220/125	7
15	F	34	RH	5	12·5	180/120	180/120	14
16	F	57	EH	5	30	225/120	230/125	5
17	F	59	EH	5	15	210/120	220/135	3
18	F	73	EH	5	5	210/120	205/120	11
19	M	47	EH	10	35	240/140	200/140	5

Abbreviations as in Table 1.
* Patients given 1 g. of chlorothiazide.

improved; atrial sounds became inaudible in 9 cases out of 16. Fundal hæmorrhages and exudates resolved in 10 of 21 patients, and papilloedema cleared rapidly in the 3 cases of malignant hypertension. In 7 patients there was diminution in the left ventricular hypertrophy shown in the electrocardiogram; there was recovery of negative T-waves in the left precordial leads, correction of ST-segment depression, in the absence of digitalis or ischæmia, and/or reduction of abnormally high R-wave voltage in lead V_5 (Fig. 1).

The effect of treatment on the hypertensive complications is also shown in Fig. 2 separately for the patients who responded by a drop of diastolic pressure of at least 10 mm. Hg and for those who did not respond to treatment. This

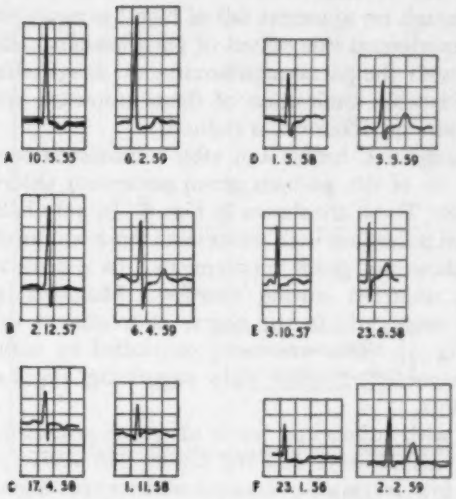

FIG. 1.—Lead V_5 of the electrocardiogram illustrating improvement in the cardiographic picture in 6 patients, referred to as A, B, etc. The dates of recording are indicated, and in each case the right-hand tracing reflects the effect of treatment.

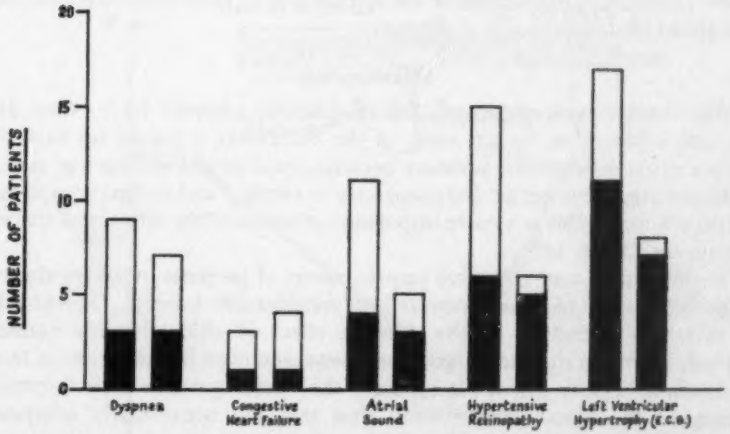

FIG. 2.—Incidence of hypertensive cardiovascular features before and after treatment in patients who responded to therapy (left-hand column), and those who showed poor or no response (right-hand column). The upper limit of each column represents the number of patients in whom the sign or symptom was present initially. The unshaded portion indicates those in whom the features improved or disappeared and the lower shaded segment the number of cases in whom they were still present at the final examination.

illustration shows that a small number of the latter patients showed some improvement, although no apparent fall of blood pressure occurred.

All patients experienced side effects of ganglion-blockade which could be partially relieved with the parasympathomimetic drugs which were given in every case. Considerable diminution of these untoward symptoms occurred when the dose of mecamylamine was reduced.

Serum potassium levels before and after administration of chlorothiazide were available in 10 of the patients given potassium chloride and in 4 not taking supplements. These are shown in Fig. 3. In only half the patients was there a fall in serum potassium with treatment; there was no difference between those given and those not given supplements. In 4 patients a small rise of serum potassium occurred during therapy. Muscular weakness due to hypokalæmia was seen early in the course of treatment with chlorothiazide in one patient (Fig. 4). This was easily controlled by withholding the drug temporarily. Electrocardiographic signs suggesting hypokalæmia were seen in two other patients.

Of 5 patients with subnormal levels of serum potassium before therapy, 3 had malignant hypertension and the fourth had severe retinopathy. This relation between low levels of potassium and severe degree of hypertensive retinopathy has been previously noted (Hilden and Krogsgaard, 1958). The blood urea was under 50 mg. per cent. in all patients and the final levels did not differ more than 15 per cent. from the initial ones in either direction.

Doyle *et al.* (1956) and Smirk and McQueen have said that little, if any, tolerance to mecamylamine developed, but gradual occurrence of tolerance has been recorded (Sears *et al.*, 1959) and this was found in the present series (Tables 1 and 2). Chlorothiazide did not appear to have influenced the degree or the speed of development of tolerance.

Discussion

With the regimen employed, fall of diastolic pressure by 10 mm. Hg or more was achieved in 70 per cent. of the cases over a period up to 3 years; in 53 per cent. the diastolic pressure became equal to or less than 100 mm. Hg. Significant improvement or disappearance of cardiac and retinal complications was also observed; this is a more important criterion of the efficacy of treatment (Hagans and Brust, 1960).

The subjective and objective improvement of patients in whom there was no significant drop of blood pressure is of considerable interest. The possibility that this was secondary to the diuretic effect of chlorothiazide cannot be excluded, although similar improvement was seen even in the course of therapy with mecamylamine alone. It is likely that these patients had intermittent lowering of the blood pressure and that this was occasionally adequate to ensure significant benefit (Leishman, 1959).

With addition of chlorothiazide, it was possible to maintain control with approximately 45 per cent. of the previous amount of mecamylamine; a significant decrease of the incidence and severity of side effects resulted. Major difficulties with chlorothiazide were not encountered; only one patient

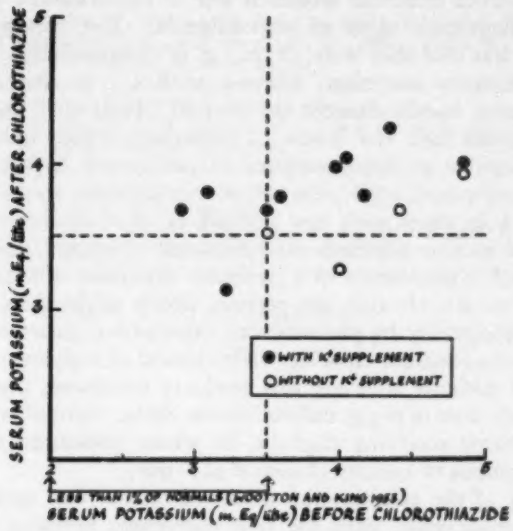

FIG. 3.—Serum potassium levels in 14 patients before and after treatment with chlorothiazide.

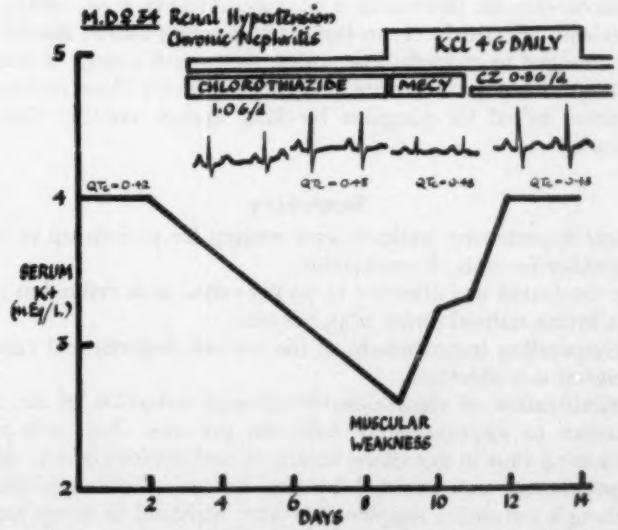

FIG. 4.—Hypokalæmia in a patient receiving mecamylamine (mecy) and chlorothiazide (cz) 1·0 g. daily. Immediate return of potassium to normal levels with reduction of chlorothiazide to 0·5 g. and increase in the dose of potassium supplements.

developed short-lived muscular weakness due to hypokalæmia and two more had electrocardiographic signs of hypokalæmia. The common feature in these 3 patients was that they were all on 1 g. of chlorothiazide; this promotes appreciable potassium excretion, whereas with 0·5 g. daily, the 24-hour potassium excretion hardly exceeds the normal (Richterich, 1959). Furthermore these patients had low levels of potassium before treatment. Since there is tendency for serum potassium to rise under hypotensive therapy (Hilden and Krogsgaard, 1958), the risk of hypokalæmia seems greater in the early stages and in cases with low normal or decreased serum potassium. Potassium supplements, although an additional safeguard, did not prevent the occurrence of hypokalæmia in 2 patients. Omission of these supplements would simplify an already complex régime, which might thus become easier to adhere to, particularly by patients who experienced gastro-intestinal upset from ingestion of potassium chloride. Withdrawal of supplements may prove feasible in most patients after the first weeks of treatment, particularly with the relatively safe dose of 0·5 g. chlorothiazide daily. Special attention should be paid to patients receiving digitalis, in whom potassium depletion may precipitate symptoms of toxicity (Lown *et al.*, 1951).

The efficacy of the combination under discussion and under out-patient conditions is encouraging, since the new adrenergic blocking agents do not satisfy criteria for ideal hypotensives (Stevenson *et al.*, 1961). The initial enthusiasm for bretylium has been subsequently moderated (Dollery, 1961) and the advantages of guanethidine are partly offset by difficulty of achieving satisfactory compromise between lowering of blood pressure and excessive hypotension on exercise (Bartorelli *et al.*, 1960; Dollery *et al.*, 1960). For these reasons patients effectively controlled with mecamylamine should not have their drug changed to guanethidine, unless they reach a stage of unresponsiveness. Furthermore a greater number of new patients than perhaps thought may be better suited for ganglion blocking agents, notably those who do physical work.

Summary

1. Thirty hypertensive patients were treated for periods up to three years with mecamylamine and chlorothiazide.

2. The treatment was effective in 70 per cent., with reduction of diastolic pressure to within normal limits in 53 per cent.

3. Corresponding improvement of the various features and complications of hypertension was observed.

4. Administration of chlorothiazide allowed reduction of the amount of mecamylamine to approximately half the previous dose, without loss of control, resulting thus in decreased incidence and severity of side effects.

5. Hypokalæmia was avoided by low dosage of chlorothiazide (0·5 g. daily), although potassium supplements were withheld in many cases.

The author is greatly indebted to Dr. J. F. Goodwin for permission to study these patients and for advice and guidance throughout the work.

REFERENCES

BARTORELLI, C., GARGANO, N., REGOLI, D., and ZANCHETTI, A. (1960): *Presse méd.*, **68**, 1827.
DOLLERY, C. T., EMSLIE-SMITH, D., and MILNE, M. D. (1960): *Lancet*, **II**, 381.
DOLLERY, C. T. (1961): *Med. Clin. N. Amer.*, **45**, 429.
DOYLE, A. E., MURPHY, E. A., and NEILSON, G. H. (1956): *Brit. med. J.*, **II**, 1209.
HAGANS, J. A., and BRUST, A. A. (1960): *Amer. J. Med.*, **28**, 905.
HILDEN, T., and KROGSGAARD, A. R. (1958): *Amer. J. med. Sci.*, **236**, 487.
LEISHMAN, A. W. D. (1960): *Brit. med. J.*, **I**, 361.
LOWN, B., SALZBERG, H., ENSELBERG, C. D., and WESTON, R. E. (1951): *Proc. Soc. exp. Biol. N.Y.*, **76**, 797.
RICHTERICH, R. (1959): *Klin. Wschr.*, **37**, 355.
SEARS, H. T. N., SNOW, P. J. D., and HOUSTON, I. B. (1959): *Brit. med. J.*, **I**, 462.
SMIRK, F. H., and MCQUEEN, E. G. (1957): *Brit. med. J.*, **I**, 422.
STEVENSON, M., GOODMAN, N., FINKELSTEIN, D., and BELLET, S. (1961): *Amer. J. Cardiol.*, **7**, 386.
WOOTTON, I. D. P., and KING, E. J. (1953): *Lancet*, **I**, 470.

Brit. J. Dis. Chest (1961) 55, 216.

THE VALUE OF CHLOROMYCETIN SUCCINATE USED TOPICALLY IN INTRATHORACIC SUPPURATION

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The efficient eradication of chronic intrathoracic suppuration has always been a serious problem. Effective surgical drainage often combined with local deroofing rib resection is essential in many cases, but in some even those measures are inadequate. Systemic antibiotics readily reach infection in the lung parenchyma, but they are much less effectual against pus in the pleural cavity. Over the years we have augmented a systemic antibiotic attack with topical instillations of penicillin, streptomycin and tetracyclines with good effect. An increasing proportion of hospital infections due to *Staphylococcus aureus* or *Staph. pyogenes* have, however, become resistant to these drugs. Where sensitivity to chloromycetin remained, it seemed logical to assess its topical efficacy in these infections.

Early reports mentioned depression of the hæmopoietic system as a possible complication of chloromycetin therapy, particularly when the drug was administered systemically for long periods (Ross, Puig and Zaremba, 1957-58). As the infected pleura is relatively avascular, there seemed less risk of an antibiotic instilled locally being absorbed to any appreciable extent. We thought it would be valuable to employ chloromycetin succinate intrapleurally in the management of empyema in conjunction with surgical treatment. Chloromycetin succinate is the sodium salt of the monosuccinate ester of chloramphenicol, it is readily soluble in water, and is intended for parenteral use by the intravenous, intramuscular or subcutaneous route.

The following is an account of our experience with chloromycetin succinate in 28 patients. All but three of these had intrathoracic empyemas occurring as either primary conditions or secondary to surgical intervention. The investigation extended over two years. This was necessary in order to collect sufficient cases, as primary empyemas are relatively rare since the advent of chemotherapy in the treatment of pneumonia. In addition empyema complicating thoracic surgery is a comparatively unusual occurrence.

The method of administration of chloromycetin was similar in each. After preliminary typing of the infecting organism and testing its sensitivities, chloromycetin succinate in the dosage of 1 g. daily was instilled either directly into the pleural cavity or into the drainage tube, which was then clamped for a period of 1-2 hours. The succinate, in the form of a powder, is easily reconstituted by the addition of 10 ml. of sterile water or saline. The duration of treatment with the preparation varied from as little as eight days to as long as ninety days. In 19 patients the organism isolated was *Staphylococcus aureus*,

(*Received for publication June* 10, 1961.)

resistant to penicillin in 17 cases, but sensitive in all to chloromycetin. Two had a coliform infection, one was infected with a pyocyaneus, one with beta hæmolytic streptococcus, and one with a mixture of coliform organisms and pyocyaneus. In four, although numerous pus cells were seen, no organism could be grown on culture.

To confirm that little or none of the drug was absorbed into the circulation, blood and urine levels were estimated in 4 patients, fourteen days after starting treatment. Oral chloromycetin was withheld from all patients during the period of investigation.

Method of Assay

After an oral dose of 2 g. chloromycetin peak blood levels (20-40 μg. ml.) are attained in approximately 2 hours (Goodman and Gilman, 1955). Within 24 hours 80-92 per cent. is excreted in the urine, and urinary concentrations are some twenty times greater than simultaneously determined plasma levels. After 12-18 hours the drug cannot be detected in the blood.

In the present investigation of levels attained after the topical use of chloromycetin, three estimations were performed in each case:

1. The serum level 1 hour after application.
2. The serum level 6 hours after application.
3. The total urinary excretion in the 24 hours following application.

The results are shown in Table I.

Table I

Case	*Sex*	*Age*	*No.*	*Serum levels in μg./ml.*		*Urinary excretion mg./24 hours*
13	M	37	13	Not detectable	Not detectable	6·9
11	F	19	11	0·4	" "	6·5
26	M	37	27	0·65	" "	14·5
24	M	28	25	0·50	0·50	3·8

The assays were performed by the method described by Levine and Fischbach (1951). This method involves extraction of suitably buffered samples of blood and urine with a chloroform-ethyl acetate mixture, reduction of the nitro group of chloromycetin to an amino group, and diazotisation and coupling with N-(1-naphthyl) ethylenediamine to form coloured solutions which are read in a photo-electric colorimeter at 558 μ.

The results show that only minimal absorption of chloromycetin occurs after topical application. The serum levels represent only 0·4 per cent. of those anticipated after a similar oral dose, and in three of the four cases chloromycetin was not detectable after 6 hours, confirming the rapid clearance of the drug from the blood stream.

The total chloromycetin excreted in the urine represents 0·6-2·3 per cent. of the figures expected if absorption from topical application approached that from the alimentary tract.

In addition, estimation of the hæmoglobin levels and of white cell counts, including differential counts, were carried out on many of the patients, particularly those on prolonged treatment, and no significant drop in either hæmoglobin or white cells was noted.

Discussion

There appear to be no previous reports in the literature on the local application of chloromycetin succinate in patients with intrathoracic suppuration. The difficulty in eradicating infection in these cases is all too obvious, as the persistence of a space or cavity inside the chest is always a potential danger. It may lead to metastatic complications, recrudescence of infection locally, rupture into a bronchus, and even empyema necessitatis. When chronic infection becomes established, amyloidosis may supervene and may lead to death from renal failure. Much can be done surgically to drain or close such a space, but the instillation of an effective antibiotic can act as a very useful adjunct.

We have used chloromycetin succinate topically for as long as ninety days and have encountered no toxic effects. This is in accord with the chloromycetin levels estimated in the blood and urine of 4 of our patients, which showed little or no absorption of the drug into the circulation. In only 1 patient was any side effect encountered, but this necessitated cessation of treatment. In this case the presence of a bronchopleural fistula allowed some of the locally instilled drug to reach the patient's mouth, and its bitter taste produced immediate vomiting.

Twenty-five of the patients in this series had intrathoracic empyemas, the remaining three had skin sepsis. Of the empyema group 11 were primary conditions and 14 followed various surgical procedures.

Of the three deaths which occurred, two were in patients with lung neoplasms, and death was attributable to widespread dissemination of the malignant process. The third occurred in a patient who had suffered from a chronic empyema and nephritis for many years. He succumbed to uræmia ten days after simple surgical drainage.

The topical use of chloromycetin is no substitute for effective surgical drainage and the administration of systemic antibiotics. We feel, however, from our experience in this series that it expedites healing in the empyema cavity, and, as proven by the blood and urine levels, it can be given for prolonged periods without risk of toxicity to the patient.

Summary

Experience in the use of the topical application of chloromycetin succinate in 28 patients is presented. Most of the cases had empyemas, and in the majority the staphylococcus was the infecting organism.

We feel that it is logical to instil chloromycetin directly into an infected space. Its lack of systemic absorption indicates that it can be given for prolonged periods without risk.

The authors wish to thank Mr. R. S. Barclay, M.D., F.R.C.S.E., F.R.F.P.S.G., Consultant Thoracic Surgeon, and Dr. L. G. Bruce, Consultant Bacteriologist, for permission to publish. We also appreciate the invaluable help afforded by Dr. A. P. Kenny, Biochemist, Victoria Group of Hospitals, in the assay of chloromycetin blood levels, and the additional information provided by Mr. E. J. Middleton of Parke, Davis and Co.

For unstinted advice and information on the application of chloromycetin and for supplies of an early prototype topical chloromycetin preparation we are indebted to Parke, Davis and Co., Hounslow, England.

REFERENCES

GOODMAN, L. S., and GILMAN, A. (1955): "The Pharmacological Basis of Therapeutics." 2nd Edition, p. 1395.

LEVINE, J., and FISCHBACH, H. (1951): "The chemical determination of chloramphenicol in biological materials," *Antibiot. and Chemother.* **1**, 59.

ROSS, S., PUIG, J. R., and ZAREMBA, E. A. (1957-58): "Chloramphenicol acid succinate (sodium salt). Some preliminary clinical and laboratory observations in infants and children," *Antibiotics Annual 1957-58*, p. 803.

Brit. J. Dis. Chest (1961) **55**, 220.

REVIEWS OF BOOKS

Treatment of Cancer and Allied Diseases. Volume 4, *Tumors of the Breast, Chest and Esophagus.* Edited by GEORGE T. PACK and IRVING M. ARIEL. London: Pitman Medical Publishing Co. Ltd. £12.

This fine book comprises carefully integrated contributions on every aspect of tumours affecting the thorax. The editors present a balanced and refreshing view of breast, pulmonary, cardiac and œsophageal growths of all kinds.

The whole work is stimulating, well and clearly illustrated. The authors comment very fairly on their subjects.

The chapters on breast cancer are well done, but the descriptions of such grossly major and serious procedures as Inter-Scapulo-Mammo-Thoracic amputation and block supraclavicular, mediastinal and internal mammary dissection with radical mastectomy leads the thoughtful reader to wonder how far such procedures are justifiable.

The place of irradiation therapy is clearly stated.

Further advances in the treatment of breast cancer are to be looked for in the field of hormone therapy, perhaps therefore the space given to descriptions of mutilating surgery might have been better used in amplification of these good chapters. For example, there is no comment on such questions as to why it is that some breast cancers respond to ablation of adrenals or pituitary and why some do not, or why some respond and then retrogress.

The sections on the treatment of lung cancer and other lesions are mostly first class. The views expressed are those of some of the most competent thoracic surgeons in the world and there can be nothing but praise for the presentation. There is some unnecessary repetition, as for instance in the description of intrathoracic lymphatics, and chapter 22A is rather superfluous. The chapters on radical lobectomy and pneumonectomy might have been considered together rather than separately.

The sections on irradiation for lung cancer are valuable and make clear the importance of accurate co-operation between surgeon and radiotherapeutist.

Not all thoracic surgeons would subscribe to the view that surgery for Pancoast's tumour is necessarily unsatisfactory. If one is prepared to sacrifice some anatomical structures, radical surgery can be surprisingly successful.

There is a particularly good chapter on heart tumours.

The chapters on œsophageal tumours are adequately illustrated and give a comprehensive survey of the surgical possibilities of this difficult subject. The various replacement techniques are made clear, but a chapter on the snags and difficulties would have rounded off this excellent and useful volume.

DONALD BARLOW.

Skelettuberkulose. Lungtuberkulose im Hohern Lebensalter. Aktuelle Probleme. Stuttgart: George Thieme Verlag. DM.21.

The Society of South-West German specialists of tuberculosis met at Bad Duerckheim from the 26th to the 28th May, 1960 to discuss tuberculosis of the skeleton.

After a concise résumé of the pathological anatomy of the disease by

Randerath, therapy was extensively discussed. The consensus of opinion is that bone tuberculosis should be treated by systemic tuberculostatics, mainly isoniazid and streptomycin, and by surgery of the affected area. Some authorities advocate lengthy preparation with isoniacid before operation, others go straight ahead and follow it by chemotherapy. The question of how to fill the cavity, referring mainly to spinal tuberculosis, is discussed in detail. Kastert advises leaving a drainage tube in position and washing out debris and caseous matter frequently with streptomycin solution. Colombani is more conservative, and merely introduces a metal tube into the tuberculous cavity, through which he drains and washes out the area with suitable solutions of tuberculostatic agents. Lerch fills the cavity with bone, either of human or of animal origin.

Kastert opens joints early, does a synovectomy and attempts to keep the joint functioning, which in later stages often proves impossible; then he advises arthrodesis with or without additional bone splints. Most speakers agree with Kastert in principle, but vary his methods in the light of personal and local experience. Statistics vary between 30 and 50 per cent. improvement rate, but different hospitals use different standards and work on different age groups.

The plea for early diagnosis is heard again. History, sensitivity to percussion, skin temperature, serial X-rays, tomograms, can all be suggestive but are not conclusive. Isolated calcification of the anterior edge of an intervertebral disk with adjoining changes is considered to be pathognomonic (Schwabe). Puncture material is only conclusive if positive bacteriological or histological evidence is obtained.

The second part of the meeting was devoted to the problem of tuberculosis in the aged. It does not differ in principle from the treatment of the tuberculosis in the younger group. Diabetes, heart disease, emphysema, gastrointestinal disease and psychological disturbances play a greater part in patients over fifty years of age and have to be dealt with parallel with the pulmonary disease. Hausser discussed the surgical aspect of pulmonary tuberculosis and advised caution in the elderly. Schneider spoke about the disease in the general practice and concentrated upon protection of contacts and chemotherapy. Kunz discussed gastric complication and Weicksel superinfection with fungi.

The meeting did not suggest any radical changes in diagnosis or treatment of skeletal tuberculosis, nor in the tuberculosis of the elderly lung, but both subjects were well reviewed and thoroughly discussed.

C. H. GOLDMAN.

Surgical Diseases of the Chest. BRIAN BLADES (Editor). London: Kimpton. Pp. 571, 267 figs., 18 contributors. £8 5s.

This book is intended to cover the whole field of thoracic surgery. It deals with pulmonary, œsophageal and cardiac diseases and their treatment, but the emphasis is in the field of cardiac surgery.

The editor has called on no less than eighteen collaborators in the production of the book, and has paid the price: the space which has been devoted to individual topics often bears little relation to their importance. Thus, that on diseases of the chest wall extends to 25 pages, and that on diseases of the mediastinum to 48, whereas the lungs and the pleura and pulmonary tuberculosis are covered in 98. Of these only 12 are devoted to bronchial carcinoma.

There are chapters on pulmonary physiology, cardiac mechanics, post-operative care, and on fluid balance, all of which are valuable. The standard of the numerous illustrations is high and the bibliography at the end of each chapter is extensive. This bibliography is however distressingly isolationist, and much of it is many years out of date (the average year for the numerous references on œsophageal and pulmonary disease is 1950).

The sections on cardiac surgery include a short historical survey of the treatment of each condition which is under consideration; these are interesting and informative, but the amount of detail which is given on the technique of the various operations is often excessive, for, as the editor says in his preface, surgery cannot be learnt from books.

Opinion about individual problems obviously varies from place to place, but there can be few physicians on this side of the Atlantic who would agree with the dosage of 1 gm. of streptomycin twice a week and 12 gm of PAS a day for the treatment of pulmonary tuberculosis, nor with the view that frequently repeated bronchoscopies may obviate the need for surgery in lung abscess.

The book is interesting in so far as it paints a picture of American thoracic surgery as it is today, but £8 5s. seems quite a price to pay for this.

J. R. BELCHER.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues.

Psychotherapeutic Techniques in Medicine. Michael and Enid Balint. London: Tavistock Publications. 21s.

Diets for Heart Patients. D. N. Phear and R. Spencer-Smith. London: Chest and Heart Association. 1s. 3d.

Night Calls—A Study in General Practice. Max B. Clyne. London: Tavistock Publications. 21s.

The Operation. Leonard Engel. London: Pan Books. 2s. 6d.

Einfuhrung in die Diagnostik und Begutachtung der Siliko-Tuberkulose. Gustav Sepke. Jena: Gustav Fischer Verlag. DM36.60.

Tuberkulose Jahrbuch 1959. Fritz Kreuser. Berlin: Springer Verlag. DM28.80.

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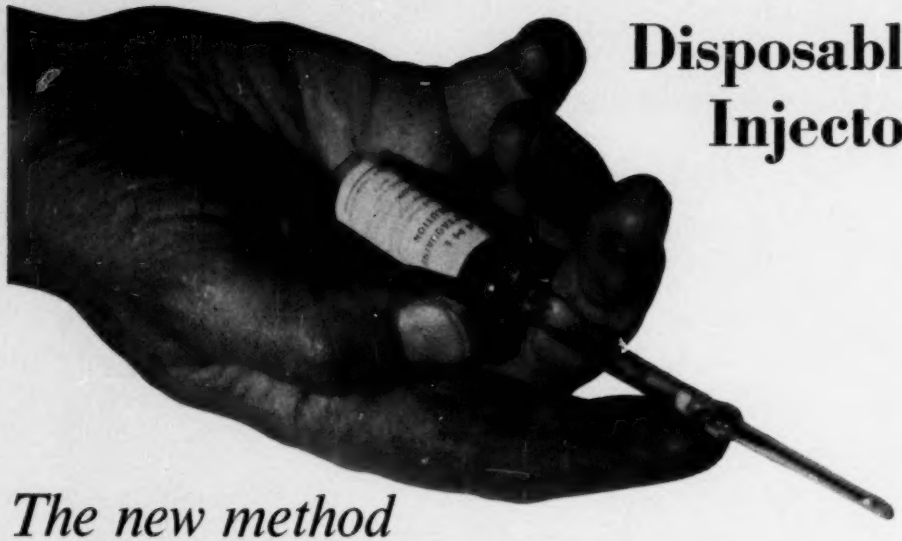

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